**A Dissertation on**

# PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETIC PATIENTS.

***Submitted to***

**THE TAMILNADU Dr. M.G.R MEDICAL UNIVERSITY**

**CHENNAI**

***in partial fulfillment of the regulations***
***for the award of the degree of***

**M.D BRANCH-I**

**GENERAL MEDICINE**


**GOVT. STANLEY MEDICAL COLLEGE & HOSPITAL**

**CHENNAI – TAMILNADU**

**APRIL 2014**

# CERTIFICATE

This is to certify that this dissertation entitled **"PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETIC PATIENTS "** submitted **by Dr. N.Sukanya** to the Tamilnadu Dr. M.G.R medical University is in partial fulfillment of the requirement of the award of M.D DEGREE (BRANCH-I) and is a bonafide research work carried out by her under direct supervision and guidance.

**Signature of the Unit Chief** **Signature of Professor & HOD**

**Signature of the Dean**

**Dr. S.GEETHALAKSHMI M.D., Ph.D**

# DECLARATION

I solemnly declare that the dissertation entitled "**PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABEIC PATIENTS"** was done by me at the Government Stanley Medical College and Hospital during 2011-2014 under the guidance and supervision of Prof. Dr.K. Madhavan M.D. The dissertation is submitted to the Tamilnadu Dr.M.G.R Medical University towards the partial fulfillment of requirement for the award of M.D. Degree (Branch-1) in General Medicine.

Place:

Date : **Dr. Sukanya N**

## ACKNOWLEDGEMENT

I owe my thanks to **Prof. S. Dr. Geethalakshmi, M.D., Ph.D.,** The Dean, Government Stanley Medical College, for allowing me to avail the facilities needed for my dissertation work.

I am grateful to **Prof. Dr. P. Vijayaraghavan, M.D.,** Professor and Head of the Department of General Medicine, Government Stanley Medical College for permitting me to do the study.

I am grateful to **Prof. Dr.K.Madhavan M.D.,** Professor, Department of General Medicine, Government Stanley Medical College for guiding me to do the study.

I express my gratitude to my unit Assistant Professors **Dr.Samuel Dinesh, Dr.Geetha,** for their valuable suggestions.

I thank all my patients for letting me to examine them and cooperated to the procedures, patiently.

I sincerely thank the ECG technicians who helped me and cooperated in my study.

# CONTENTS



**ANNEXURE**

# PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETIC PATIENTS

**BACKGROUND:** Diabetes mellitus is a global epidemic .Prevalence of diabetic cardiac autonomic neuropathy is high and it carries a high mortality rate. Early diagnosis of cardiac autonomic neuropathy helps to identify individuals at risk and prioritize the management.

**AIMS OF THE STUDY**: To study the prevalence of cardiac autonomic neuropathy in Type 2 diabetic patients by assessing the individuals by (a) Standard autonomic testing & (b) Ansiscope .

**METHODS**: Patients with Type 2 diabetes from FEB 2013 to DEC 2014 were included in the study. Patients were subjected to symptom analysis, clinical examination and laboratory investigations. Eligible cohorts were subjected to standard autonomic testing and testing with Ansiscope. Standard autonomic testing includes (a) Assessing heart rate variability with deep breathing, valsalva, supine to standing position.(b) Assessing blood pressure variability with supine to standing position. Patients were categorised based on Ewing's criteria for CAN.

**RESULTS**: 19% (n=16)of the study group individuals were newly detected $T_2$DM. Among them 11 individuals 68.8% were CAN positive by ansiscope and 81.2 % (13 subjects) by conventional method. 50 individuals were diabetic for a duration 1-5 years. Among them 82% (41 individuals) and 88%(44 subjects) tested positive for autonomic dysfunction by ansiscope and conventional method respectively. 18 subjects who were diabetic for more than 5 years tested 100% positive for autonomic dysfunction by both the methods.

**CONCLUSION**: The prevalence of cardiac autonomic neuropathy is extremely high among diabetics. Poor blood sugar control is significantly associated with CAN . Also individuals who are unaware of the complications of diabetes have shown a significant association with autonomic dysreflexia. Early screening, early diagnosis, proper education of patients and strict glycemic control help in the arrest of progression of Cardiac Autonomic Neuropathy in Type 2 diabetic population.

**KEYWORDS:**
Diabetes, cardiac autonomic neuropathy, Ansiscope, autonomic testing, Ewing's criteria.

# INTRODUCTION

## DIABETES: A CHALLENGE OF 21st CENTURY

Change in the lifestyle of people along with globalization in the past century has increased the incidence of diabetes. Findings of a report by Ramachandran et al has proved **(1)**urbanization of India causing a high prevalence of diabetes.It has increased from 13.9 in 2002 to 18.2 in 2006 in urban areas. The rural area also showed a increase in prevalence from 6.4 in 2002 to 9.2 in 2006. According to International Diabetic Federation diabetes atlas, **(2)**India is next only to china hosting the high number of people with diabetes. The number of people with diabetes is expected to increase from 65.1 million in 2013 to 109 million in 2035 in India .. Indians develop diabetic complications at an early age. This results in increase in mortality and morbidity among Indians. Despite a high prevalence of diabetes in South -east Asian countries only 5 % of the global health care cost goes towards diabetes care. Prevention of complications associated with diabetes is achieved by primary prevention by modifying risk factors such as insulin resistance and obesity.**(4)**

Type 2 diabetes is a disorder characterized by insulin resistance, relative decrease in insulin secretion and hyperglycemia. Environmental and genetic factors play a role in the development of diabetes

Diabetic neuropathy a set of clinical syndrome sometime silent and undetected, may be single or combined with signs which are non specific, insidious and slow and often diagnosed by exclusion. Neurologic complications occur equally in all types of diabetes – type I, type II and all other types of diabetes**(19).**

One fourth of patients attending diabetes clinic had diabetic neuropathy based on the symptoms present. A simple clinical examination like testing for ankle jerk or vibration test revealed a positive test in 50% of individuals. A more sophisticated test for autonomic neuropathy showed a 90% incidence of neuropathy in diabetic patients at diagnosis **(21)**

Diabetic neuropathy is the most common cause of hospitalization than other known cause of complications **(22).** So early diagnosis of cardiac autonomic neuropathy by using simple non invasive investigation – heart rate variability using ECG helps in the identification of individuals at risk.

This study aimed at assessing the prevalence of Cardiac Dysautonomia in type 2 diabetic individuals using conventional testing methods and by using mathematical instrument- Ansiscope

# AIMS OF THE STUDY

1. To study the prevalence of cardiac autonomic neuropathy in Type 2 diabetic patients by assessing the individuals by

    a. Standard autonomic testing and

    b. Ansiscope

at Government Stanley Medical College and Hospital, Chennai.

2. Early diagnosis of cardiac autonomic neuropathy helps to identify individuals at risk and prioritize the management.

# REVIEW OF LITERATURE

## DIABETES:- A GLOBAL TSUNAMI

Type 2 diabetes is a disorder characterized by insulin resistance, relative decrease in insulin secretion and hyperglycemia. Environmental and genetic factors play a role in the development of diabetes.

## CLINICAL RISK FACTORS

Individuals whose are mother is a diabetic has a 5-6 fold increased risk of developing diabetes**(5,6).** Family history in a first degree relative increases the risk by about 2 to 3 times. Asians or African Americans are more susceptible than whites.**(7)** Obesity is a major risk factor in type 2 diabetes as it increases peripheral insulin resistance **(8)**

Life style factors like decreased physical activity, high fat diet, smoking ,alcohol and obesity play a pathogenic role **(9)**

Smoking has a definite relationship**(10)** with development of diabetes. Sleep duration has a definite relationship to the development of diabetes.**(13)** Both inadequate sleep of less than 5 to 6 hrs /day and excess sleep of more than 8 hrs /day is associated with increased risk of

diabetes. Disruption of sleep produces low melatonin secretion which increases the risk of developing diabetes.**(14)**

Dietary patterns like increased intake of sweets ,high fat dairy products, red meat, processed meat are associated with increased risk **(15)** Sugar sweetened soft drinks , producing weight gain, deficiency of vitamin D, Selenium**(16)**chromium**(17)** have a role in the development of diabetes. Women who had gestational diabetes, patients with heart failure, MI, hyperuricemia, polycystic ovary syndrome are associated with increased risk of becoming diabetic.

**ADA Criteria for the diagnosis of diabetes (18)**

1. HbAIC >=6.5 % OR

2. Fasting plasma glucose >= 126 mg/dl . (Fasting is taken as no energy intake for 8 hours at least ) OR

3. 2hour plasma glucose >=200 mg/dl in an OGTT. ( to be done using a 75 g glucose load) OR

4. In a patient with classic symptoms of hyperglycemia, a random plasma glucose >= 200 mg/dl

## DIABETIC NEUROPATHY

Ziegler et al. in a cohort of type I and Type II diabetic patients showed that type I diabetic was associated with 25% and type II diabetic with 35% risk of autonomic neuropathy using variability of the heart rate and spectral analysis of the R-R interval. **(23)**

San Antonio convention **(24)** has classified neuropathy into

1. Sub clinical neuropathy - detected with electro diagnostic testing

    a. nerve conduction studies
    b. abnormal quantitative sensory test
    c. quantitative autonomic test

2. Diffuse clinical neuropathy

    a. distal symmetric sensory motor neuropathy
    b. autonomic neuropathy.

3. Focal syndrome

    a. Mononeuropathy-median, ulnar, peroneal nerve involvement.
    b. Cranial mononeuropathy - VII, III, IV, VI cranial nerves involvement
    c. Mononeuropathy multiplex
    d. Plexopathy
    e. Polyradiculopathy

## NATURAL HISTORY OF NEUROPATHY

Two distinct groups of neuropathies exists

1. Sensory and autonomic neuropathies that keeps progressing

2. Focal and acute painful neuropathies that tends to regress

**Poor blood sugar control is the major risk factor for progression of neuropathies. (25)**

There is a steady rate of deterioration of Nerve Conduction Velocity(NCV) at the rate of 1 m/sec/yr in type 2 diabetics after diagnosis . In type 2 diabetics peripheral neuropathy may be present even at diagnosis **(26)** or may precede the diagnosis of diabetes.

Distal symmetric sensory motor polyneuropathy is the most common type in diabetics. **(27)**Small fibre involvement occurs earlier. Patients present with positive symptoms like pain and burning sensation. Later in the course of disease numbness and paresthesia may develop . Large fibre involvement is characterized by ulcers and gangrene of the foot.

**Clinical screening test for diabetic peripheral neuropathy**

**VIBRATION TESTING :** 128 Hz tuning fork is used for testing. It is tested over the dorsum of great toe and other bony prominences. Graded tuning fork may also be used.

Biothesiometer is an electronic tuning fork which based on the voltage used allows vibrations to be adjusted . The lowest voltage that a normal person can sense is 6 volts in individuals less than 30 yrs and 20 volts in age 75 yrs and above. The lowest voltage perceived is called vibration perception threshold

**PRESSURE SENSATION TESTING**: 10 g monofilament also called Semmes Weinstein monofilament **(29)** is used to assess the pressure sensation. The monofilament is placed at right angles to the skin on the plantar surface of the foot. Pressure is increased until the filament buckles indicating a 10 g pressure applied. Sites to be tested are plantar surface of great toe , metatarsal heads, heel, dorsum of great toe .

**PAIN /TEMPERATURE TESTING:** pin prick sensation and hot cold sensation to be tested

## NERVE CONDUCTION STUDIES

Demonstrates axonal degeneration and decrease in compound muscle action potential. Electrophysiological abnormalities are characteristic of large fibre neuropathy .

## SMALL FIBRE AND LARGE FIBRE NEUROPATHY

SMALL FIBRE NEUROPATHY

1. Pain – superficial and burning type
2. Abnormal warm sensation
3. Abnormal autonomic function like dry skin , cold feet , decreased sweating , gastric and genitourinary disturbances .
4. Normal muscles strength and deep tendon reflexes
5. Nerve conduction studies – normal

LARGE FIBRE NEUROPATHY

1. Abnormal vibration and joint position sense
2. Decreased / absent deep tendon reflexes
3. Deep , vague , dull , crushing or cramp like pain
4. Numbness , cotton wool sensation feet

5. Sensory ataxia

6. Small muscle wasting of feet

7. Hammer toes , pes equinus deformity

8. Warm feet due to increased blood flow

## CLINICAL FEATURES OF DIABETIC AUTONOMIC NEUROPATHY

### Cardiovascular System

- Resting tachycardia
- Orthostatic hypotension
- Exercise intolerance
- Silent myocardial ischemia

### Gastro Intestinal System

- Constipation
- Diarrhea
- Esophageal dysmotility
- Gastroparesis diabeticorum
- Fecal incontinence

**Genitourinary System**

- Erectile dysfunction
- Retrograde ejaculation
- Neurogenic bladder (diabetic cystopathy)
- Female sexual dysfunction (e.g., loss of vaginal lubrication)

**Metabolic**

- Hypoglycemia-associated autonomic failure
- Hypoglycemia unawareness

**Sudomotor**

- Anhidrosis
- Heat intolerance
- Dry skin
- Gustatory sweating

**Pupillary**

- impairment of pupillomotor function impairment decreased diameter of dark adapted Pupil
- Argyll-Robertson pupil

**The differential diagnosis of DAN involves excluding the following conditions:**

a. Addison's disease and hypopituitarism

b. Pheochromocytoma

c. idiopathic orthostatic hypotension

d. Shy Drager syndrome - multiple system atrophy with autonomic failure

e. Hypovolemia

f. Medications - anticholinergic, sympatholytic effects with insulin, vasodilators

g. sympathetic blockers

h. Peripheral autonomic neuropathies idiopathic autonomic neuropathy, amyloid neuropathy.

## ASSOCIATION OF PERIPHERAL AND CARDIAC AUTONOMIC NEUROPATHY

Peripheral neuropathy is classified as small and large fibre neuropathy. Small fibre neuropathy presents as painful neuropathy where as large fibre affection presents as painless neuropathy and foot

ulcers.painful small fibre neuropathy is associated more with autonomic dysfunction**. (35)**

Llunch et al has studied autonomic dysfunction in type 1 diabetes. Frequency of autonomic dysfunction is more in type 1 diabetics and the prevalence increases with presence of peripheral neuropathy and increased duration of diabetes**(36)**

Another study conducted by rajiv et al has demonstrated that painful distal sensory neuropathy is associated with greater autonomic dysreflexia than painless neuropathy. CAN was assessed by frequency domain spectral analysis of HRV and somatic neuropathy by detailed neurophysiological testing. **(37)**

Pain and autonomic sensation is carried via small myelinated and unmyelinated nerve fibres as against vibration and touch carried by large fibres. Hence small fibre neuropathy is associated with painful DSN and Autonomic involvement.

Important clinical implication is that patients presenting with painful DSN should be assessed for autonomic dysfunction also for early detection.

# DIABETES AND HEART

## 1. DIABETIC DYSLIPIDEMIA

Atherogenic dyslipidemia is characterized by

- Increased VLDL
- increased small LDL
- decreased HDL

This triad of lipid abnormalities is atherogenic and produces premature CHD. Most of these patients are insulin resistant**.(38)**

## 2. HYPERTENSION

Hypertension is a independent risk factor for CAD, stroke, nephropathy**(39)**

Some studies have shown a positive association of HT with insulin resistance**(40)**

## 3. PROTHROMBOTIC STATE

Patients with metabolic syndrome are prothrombotic. **(41)** Patients with insulin resistance have raised levels of fibrinogen, plasminogen activator inhibitor – 1**(42)**

## 4. CARDIAC FAILURE

diabetic patients have increased incidence of heart failure with preserved systolic function as shown in Framingham heart study. Possible mechanisms

- Atherosclerosis
- Obesity
- Persistent hyperglycemia
- Sustained hypertension
- Microvascular alterations
- Altered myocardial proteins

Mortality rates of diabetics with cardiac failure is high **(43)**

## 5. DIABETIC CARDIOMYOPATHY

Ventricular dysfunction that occurs per se in diabetics in absence of associated ischemia or HT. Probable mechanisms could be altered myocardial metabolism, microangiopathy.

## 6. CORONARY ARTERY DISEASE

Both type 1 and type 2 diabetes are independent risk factors for CHD**.(44)** premature aherosclerosis and associated metabolic syndrome

play a role. Due to associated cardiac denervation and dysautonomia silent myocardial infarction is common. **(45)**

## 7. CARDIAC AUTONOMIC NEUROPATHY

CAN as outlined elsewhere is associated with exercise intolerance, intraoperative lability, postural hypotension and silent myocardial infarction.

## CARDIAC AUTONOMIC NEUROPATHY

### Anatomy

### Sympathetic nervous system

Preganglionic fibres arise from lateral column of spinal cord. They synapse in the lower three cervical and upper three thoracic ganglion. The post ganglionic fibres forms the deep cardiac plexuses. They travel along arteries and are formed in the outer wall of blood vessel, atria, ventricles , SA- AV node and cardiac myocytes.

### Parasympathetic nervous system(PNS)

PNS originates from medial medullary sites – nucleus ambiguous, dorsal motor nucleus of vagus, nucleus tractus solitarius. These are under control of hypothalamus. The vagal nerve, main parasympathetic innervations of heart exits from the medulla and enters the carotid

sheath penetrates the chest and synapses within the chain of ganglion located in the cardiac fat pads and the post ganlionic fibres supply the heart mainly SA and AV nodes. While the atrial musculature is also innervated by vagal efferents ventricular myocardium Is only sparingly innervated.

**Sympathetic activation**

Mediated by alpha receptors- causes

1. Positive chronotrophic effect( increased heart rate)
2. Positive inotrophy (contractility)
3. Positive dromotrophy ( conduction velocity via B1 receptor)
4. Increase lusitropy (rate of relaxation)

**Parasympathetic activation**

Mediated by muscuranic receptors causes

1. Negative chronotrophy and dromotrophy
2. Negative inotrophy and lusitrophy in atria

**Sympathetic and parasympathetic interaction**

In the resting state vagal tone predominates. Efferent vagal activation inhibits sympathetic activation. During exercise sympathetic tone overtakes.

Chronic hyperglycemia produces distal dying back neuropathy in peripheral nerves. Similar to this the longest autonomic nerve vagus is affected. Hence CAN in diabetes is characterized by early affection of parasympathetics and compensatory augmentation of sympathetic tone. Later in the course parasympathetic imbalance develops. **(46)**

## CLINICAL MANIFESTATIONS

### 1. Exercise Intolerance

Kahn et al studied persons with and without CAN. He showed a decreased response in blood pressure and heart rate in individuals with CAN. **(48)**

Roy et al showed decreased cardiac output with exercise in persons with CAN**(49)**

Exercise induced heart rate increase and maximum heart rate increase achieved with exercise is inversely related to the severity of CAN

Cardiac autonomic dysreflexia produces reduced exercise tolerance, decreased cardiac ejection fraction, systolic and diastolic dysfunction.

## 2. Cardiovascular Liability During Intraoperative Period

Burgos et al described need for increased vasopressor support in diabetics with autonomic dysreflexia**(50)**

Kitamura et al has shown increased hypothermia during intra operative period in patients with CAN.**(51)**

Sobotka et al has demonstrated decreased hypoxia related ventilatory drive in individuals with CAN. **(52)**

Patients with CAN anaesthesia related vaso dilatation is not compensated by autonomic response of vaso constriction and increase in heart rate.

Intraoperative reduction of core temperature causes decrease in metabolism of drugs and impairs healing of wounds.

## 3. Orthostatic Hypotension

A decrease in systolic pressure of more than 20mmhg and diastolic of more than 10 mmhg from supine to standing posture is called as orthostatic hypotension

1. In response to change in posture there is stimulation of sympathetic nervous system by activation of barorecepyor reflex and there is release of norepinephrine which causes splanchic vasoconstriction and a raise in blood pressure . in diabetics efferent sympathetic are damaged and blunting of this response associated with a decreased total vascular resistance produces a postural fall in blood pressure .

2. Also associated extravascular fluid retention due to cardiac and renal failure produces a reduction of blood volume .

3. Insulin per se has hypotensive action

4. Splanchnic vasodilation associated with post prandial state

5. decreased cardiac stimulation and decreased cariac output has a role.

**Symptomatology**

a. light headedness , black outs, presyncope

b. dizziness, easy fatigue, blurring of vision , neck pain

## 4. Silent Myocardial Infarction

Ambepityia et al had studied perception of angina pain threshold in persons with and without diabetes . He had also assessed the autonomic function tests in these individuals. He had documented a decreased angina pain perception in persons with diabetes and also had correlated this association with presence of autonomic neuropathy in these individuals . **(53)**

Vinick et al has documented a definitive relation between CAN and silent MI **(54)**

In DIAD study (detection of ischemia in asymptomatic diabetics) 1123 patients were studied and CAN was found to be a strong predictor of silent MI and cardiovascular deaths in diabetics **. (55)**

Detection of CAN is essential in diabetics as they continue to exert despite developing myocardial ischemia as they do not perceive the pain.

**Causes**

1. Cardiac denervation due to autonomic nervous system involvement

2. Decreased sensitivity to pain perception

3. Altered pain thresholds

4. Impaired neuronal activation and signal transmission from thalamus to frontal cortex

Diabetics with CAN present with following **atypical features** like cough, dyspnoea, unexplained Fatigue, atypical chest pain,only ECG changes,nausea /vomiting, edema.haemoptysis

a. Diaphoresis

b. Arrhythmias

c. Confusion

A high index of suspicion needed by treating physician

Also in type 1 diabetic patients presence of CAN is associated with early development of diastolic dysfunction and cardiomyopathy **(56)**

**5. Increased Risk of Mortality**

Ewing et al has documented a 27 % increase in 5 year mortality rate in diabetic patients with CAN as against 15 % increase in mortality in those without. Most deaths were due to renal failure and sudden

cardiac death. Patients with CAN and gastric autonomic symptoms and orthostatic hypotension had worse prognosis.

O'Brein had noted a mortality rate at 5 year in patients with autonomic dysreflexia as 27 % and those without as about 8% **(57)**

Rao et al has documented CAN as a independent risk factor for mortality rate prediction % **(58)**

Two population based studies, namely Orchard et al and Hoorn study which assessed association of CAN and mortality in type 1 and type 2 diabetic population respectively have shown significant association between the two. **(59)**CAN is also associated with major cardiovascular end points like cardiac failure, myocardial infarction , arrhythmias, angina pain and need for revascularization procedures .

Causes of high mortality associated with CAN

a. Poor hypoxia induced respiratory stimulation

b. Increased sympathetic tone and lack of nocturnal dipping of blood pressure

c. Disturbance in circadian pattern of sympathovagal response is associated with left ventricular hypertrophy

d. Lethal arrhythmias induced by asymptomatic ischemia/infarction

e. QT prolongation associated with autonomic dysreflexia predisposes to various rhythm disturbances.

f. Increased incidence of LV dysfunction and cardiac failure in diabetics with neuropathy

g. Hypoglycemic unawareness decreases threshold for arrhythmias.

h. Hypoglycemia affects autonomic nervous system in diabetics

**6. CAN associated with increased mortality in post MI patients**

Autonomic dysfunction predisposes to various arrhythmias post MI. Fava et al has documented this **(60)**

Katz et al has tested 1 min HRV with deep breathing in post MI patients to assess CAN is a good predictor of mortality post MI **(61)**

**7. Stroke**

Incidence of ischemic stroke is high in diabetics associated with cardiac dysreflexia and is an independent predictor of cerebrovascular events.

Toyry et al has demonstrated this association in diabetic population **(62)**

## NATURAL HISTORY OF PROGRESSION OF CAN

a. Usually parasympathetic dysfunction precedes sympathetic but this may not be always true.

b. Autonomic dysfunction can be detected at diagnosis in type 2 diabetes.**(63)**

c. Age, type of diabetes and to some extent duration of diabetes do not correlate with the development of CAN.**(64)**

d. Pivotal role in development and progression of CAN is mainly by the glycemic control in the patients **(65)**

e. Intense glycemic control delays the onset and also delays progression of autonomic dysfunction**(66)** Orthostatic hypotension due to sympathetic derangement is a late manifestation

f. Diabetic nephropathy is strongly associated with CAN **(67)**

g. Type 1 and type 2 diabetes may have a difference in rate of progression

h. Mortality rates due to CAN is more in type 1 diabetics than type 2 as there is a long latent period before diagnosis in type 2 .

## PATHOGENESIS

Free radicals -a free radical is a species which has one or more unpaired free electron in its orbit.

### Mechanism of generation of oxygen free radicals

Electron transfer reactions like hydroxyl radicals , superoxide anion radical, lipid alkoxyl and peroxyl radical and hydrogen peroxide generate free radicals.

Energy transfer reactions like triplet carbonyl compounds and singlet oxygen are also involved in generation of free radicals

### Hyperglycemia Induced Mitochondrial Superoxide Production

During electron transfer in respiratory chain a proton gradient is created by extrusion of protons into inter membrane space of mitochondria

This gradient stimulates ATP synthase. In diabetes with high intracellular glucose concentration, more glucose is oxidized via citric acid cycle and electron donors like NADH,FAD H2 gets used up. After a critical threshold the electron transfer inside complex 3 gets blocked. This process produces electron to get backed-up to co enzyme Q which donates electron to oxygen producing superoxide anion.

Hyperglycemia activates other pathways like redox changes, NADPH oxidases and uncoupled eNOS gets amplified and produce superoxide.

**Hyperglycemia Induced Mitochondrial Superoxide Production-Activates Other Pathways By Inhibiting GAPDH**

Intracellular hyperglycemia reduces the glycolytic enzyme GAPDH. This causes other glycolytic intermediates to increase

1. High levels of glyceraldehydes 3 phosphate – glycolytic metabolite activates following two pathways.

a. AGE pathway - glyceraldehydes 3 phosphate is the source for AGE precursor methyl glyoxal.

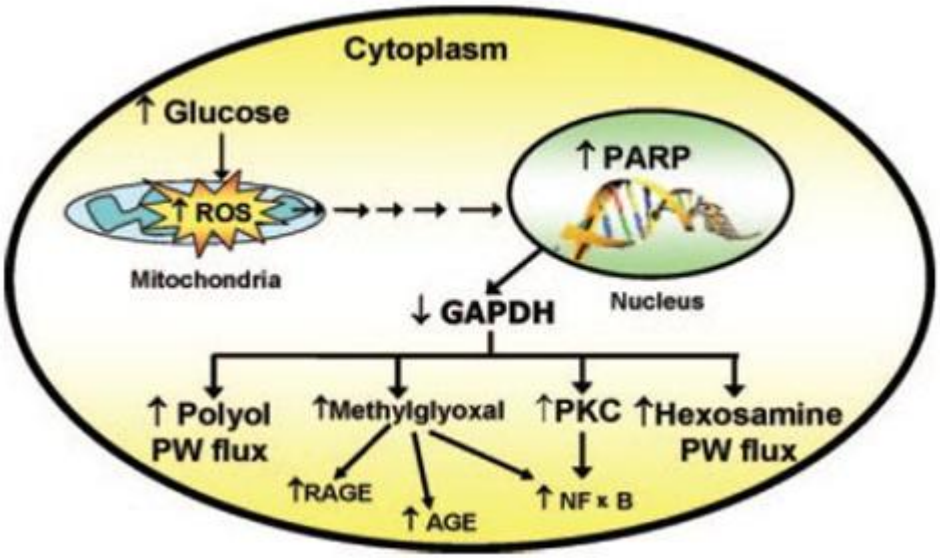
b. Classic protein kinase C (PKC)pathway : glyceraldehydes 3 phosphate is the source for diacyl glycerol which is the activator of PKC pathway

2. Levels of fructose 6 phosphate increase which is a glycolytic metabolite activates hexose amine pathway to form UDP-GlcNAc.

3. GADPH inhibition also increases the intracellular glucose level which enters polyol pathway.

a. Sorbitol is formed from glucose by the enzyme aldolase reductse consuming NADPH. Increased sorbitol is neurotoxic causing Schwann cell damage by increasing cell osmolarity.

b. Depletion of NADPH in the above process decreases intracellular myoinositol which interfere with cellular metabolism.




***Mechanism of hyperglycemia induced cellular damage***

Cellular injury due to increased reactive oxygen species

1. Oxygen free radicals attack the iron – sulfur moiety of enzymes and proteins and inhibit them. the proteins more susceptible for inhibition are complexes I-III of electron transfer chain, biotin synthase and aconitase of citric acid cycle.

2. Lipids in membranes of mitochondria, plasma and endoplasmic reticulum undergoes peroxidation. The end products of this process- lipid peroxides are toxic to the cell.

3. Proteins and nucleic acid in the cells undergo peroxidation and nitrosylation which are toxic to the cell.

4. Oxidative modification of various transcription factor causes reduced expression of anti apoptic proteins like Bcl -2 and increase in proapoptic proteins.

5. Oxidative damage of DNA especially in non dividing cells like neurons affect axonal transport and signaling resulting in loss of function of neurons.

**NRF2 and Oxidative Stress**

NRF2 is a transcription factor protects against oxidative stress. NRF2 expression is down regulated in diabetic nerves. DRG neurons are protected from free radical injury via NRF2 activation. Hence hyperglycemia induced down regulation of NRF2 makes Schwann cells and DRG more susceptible to oxidative stress.

## Role Advanced Glycation End Products in the Pathogenesis of Diabetic Neuropathy

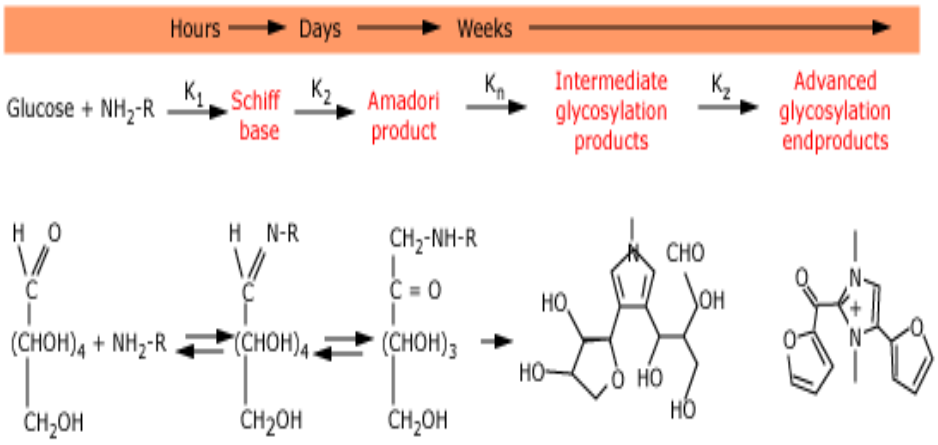
### AGEs

AGE are heterogenous compounds which are formed by non enzymatic glycation and oxidation of proteins and or lipids with aldose sugars.

### Formation of AGE

Aldehyde of glucose combines with amino acid side chain and forms covalent bond which is labile. Early glycation produces Schiff basis which are reversible. These undergo further glycation and amadori rearrangement to produce irreversible AGE products.

EXAMPLES: Pentosidine, Glycated HbA1C, N-carboxy methyl lysine, Methylglyoxal




***Formation of advanced glycation end products***

**Receptor for Age (RAGE)**

RAGE belongs to immunoglobulin receptor super family. They are expressed minimally in normal non diabetic tissue and vessels. Chronic hyperglycemia produces more AGE products which by feedback mechanism up regulates RAGE expression. RAGE stimulation produces pro inflammatory response.

**AGE on Function of Extracellular Tissue**

1. AGE produces cross linking of elastin and type I collagen there by producing increase stiffness of vessels .

2. AGE interaction via RAGE decreases binding heparin sulfate, a proteo glycan in the vessel wall to the basement membrane producing a procoagulant state.

3. Glycation of LDL decreases nitrous oxide thereby decreasing vaso dilatation.

4. Glycated LDL decreases clearance and uptake of LDL producing a pro atherogenic state promoting smooth muscle cell proliferation and atheroma formation in endo neurial vessels

**AGE on Function of Intra Cellular Milieu**

1. Glycation of FGF affects vascular homeostasis.

2. AGE induced stimulation of monocytes and endothelial cells causes increased expression of E-selectin,VEGF,VCAM-1, ICAM-1, other pro inflammatory cytokines like IL1, IL6,TNF–A, RAGE.

**Role of AGE in Diabetic Neuropathy**

1. AGE/RAGE induce oxidative stress that increases glycosidation products like pentosidine

2. Upregulation of nuclear product NF- kappa B and various pro inflammatory genes alter neurological function.

3. Atherosclerotic endo neureal vessels produces ischemic nerve damage.

4. Hyper glycemia induced AGE causes segmental demyelination of peripheral nerves.

5. AGE alters cyto skeletal proteins of axons like tubulin,actin, neuro filament andproduces atrophy of axons and degeneration.

6. Glycation of laminin produces reduced axonal regeneration.

7. Endo neurial deficiency of nitrous oxide affects microvasculature.

## POLYOL PATHWAY

Peripheral nerves uptakes glucose in a noninsulin dependant manner. In hyperglycemia high glucose in the nerves enter polyol pathway.

Two enzymes are involved in the above pathway.

a. Aldose reductase(AR)- in the presence of co factor NADPH reduces glucose to sorbitol.

b. Sorbitol dehydrogenase (SDH) – in the presence of cofactor NAD + forms fructose from sorbitol.

1. Depletion of NADPH by AR decreases the formation of myoinositol. Myoinositol depletion alters phosphoinositide metabolism thereby reducing Na+K+ ATPase activity and reducing nerve conduction velocity.

2. Depletion of NADPH causes reduction of nitric oxide and inhibits vascular relaxation producing chronic ischaemia.

3. NADPH is a cofactor for glutathione reductase and hence its depletion produces oxidative injury.

4. Sorbitol oxidation by SDH produces NADH from NAD+. NADH acts as a substrate for NADH oxidase to produce ROS.

5. Fructose formed is converted to 3 deoxy glucasone and fructose 3 phosphate. These are extremely potent nonenzymatic glycation agents. AGE acts via RAGE causing oxidative stress.

**PROTEIN KINASE C PATHWAY**

Hyperglycemia increases diacyl glycerol which activates PKC. Active PKC increases expression of TGF B and other pro inflammatory cytokines which produces oxidative damage of the diabetic nerves.

**HEXOSAMINE PATHWAY**

Fructose 6 phosphate is converted to glucosamine 6 phosphate by hexosamine. Increased flux through this pathway causes PKC activation and inflammatory cytokines over expression.

**ROLE OF ISCHAEMIA IN THE PATHOGENESIS OF DIABETIC NEUROPATHY**

**Nerve- Vascular Supply**

A. Intrinsic system- micro vessels within endoneurium

B. Extrinsic system – nutritive arteries, arterioles and epineurial vessels

There are extensive anastomosis between the two systems thereby preventing neural ischaemia.

Diabetic nerve tissues demonstrate many endoneurial abnormalities of micro vessels like

a. Thickening of basement membrane

b. Proliferation of smooth muscle

c. Swelling and proliferation of endothelial cell

d. Platelet thrombi

Pathways involved in ischaemic nerve damage

a. AGE induce various cytokine and growth factors from macrophage resulting in atheroma and obstruction of vessels

b. Hypoxic insult further stimulate oxygen free radical production, lipid peroxidation thrombaxane increase decrease in prostacyclin producing vasoconstriction

c. Polyol pathway results in production of sorbitol which affects prostcyclin production and sodium pumpand depletion of NADPH thereby decreasing NO production.

d. Nerve Growth Factor(NGF) are produced in the peripheral organs and reach the cell bodies of neuron by retrograde axon transport. NGF are essential for nervous system regeneration and endurance. Chronic hyperglycemia blunts the above response.

**CLINICAL SIGNS OF CAN**

**HRV –Impaired**

a. Earliest sign

b. Beat to beat variation is a function of integrity of sympathetic and parasympathetic activity.

c. Heart rate varies in response to normal respiration producing sinus arrhythmias which disappears with ANS dysfunction

**Resting Tachycardia**

a. Parasympathetic dysfunction produces a state of increased sympathetic tone which produces a increment of heart rate at rest more than 100/ min

b. But other causes like thyrotoxicosis, stress, exercise, heart failure, anaemia to be ruled out.

c. A fixed heart rate despite stress exercise indicates CAN.

**Cardiac Stress Testing**

Poor Exercise tolerance can be assessed by stress test. Individuals with CAN have decreased heart rate, BP, and cardiac output with exercise.

**Non Dipping BP at Night**

With sleep, in normal persons parasympathetic tone predominates hence heart rate and BP falls at night. But in presence of autonomic dysfunction sympathetic tone predominates and these persons are nocturnal nondippers.

These individuals develop concentric left ventricular hypertrophy.

**Orthostatic Hypotension**

a. Late manifestation

b. Damage to sympathetic vasomotor system.

light headedness, black outs, presyncope, dizziness, easy fatigue, blurring of vision , neck pain are the clinical presentations.

## TESTING OF CARDIOVASCULAR AUTONOMIC DYSFUNCTION

In 1970, Ewing et al put forth 5 noninvasive tests to assess the sympathovagal response **(74)** other causes of autonomic dysfunction like alcohol intake, drugs like diuretics, insulin, antidepressants, vasodilators, aspirin, age use of caffeine, exercise , smoking to be taken into consideration for the validity of the test.

**Test for parasympathetic system assessment**

a. Heart rate response to deep breathing

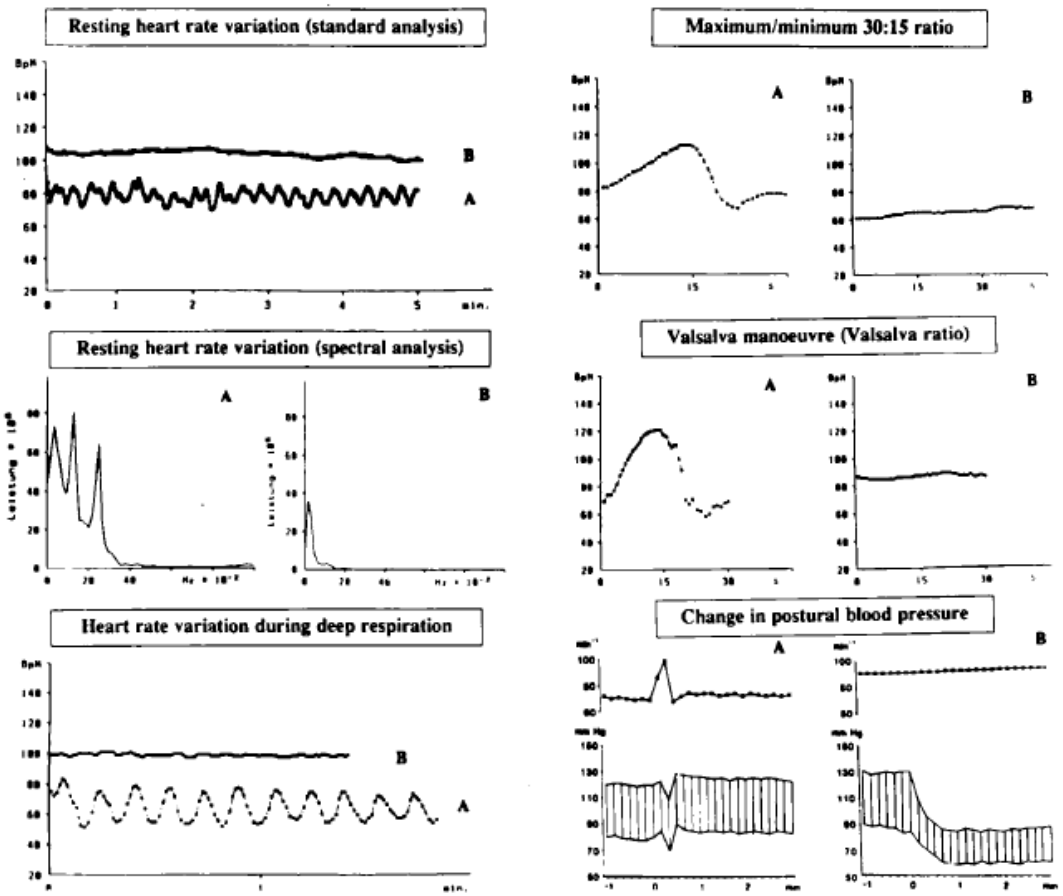
b. Heart rate response to valsalva maneuver

c. Heart rate response to standing

**Test for parasympathetic system assessment**

a. Blood pressure response to standing

b. Blood pressure response to sustained hand grip




***Tests for detection of cardiac dysautonomia***

***A. healthy subject B. diabetic patient with CAN***

## HEART RATE RESPONSE TO DEEP BREATHING

R-R variation with respiration depends on parasympathetic system. The patient is made to lie supine comfortably and asked to breathe in and out deeply at a rate of around 6 breaths per minute. This rate is chosen as maximum beat to beat heart rate variation is documented at this respiratory rate. Following measures of R-R variation are available

a. Standard deviation

b. Mean circular resultant

c. Expiration to inspiration ratio

d. Coefficient of variation

e. Maximum R-R interval minus minimum

f. Spectral analysis

**HEART RATE RESPONSE TO STANDING**

Heart rate variation from supine to standing is mediated via vagus.

In normal healthy individuals the maximum heart rate is achieved at about $15^{th}$ beat after standing. Maximum relative decrease in heart rate is achieved at about $30^{th}$ beat after standing. In patients with CAN this response is very slow.

Patient is made to lie down quietly and his ECG is recorded. Then he is made to stand and ECG tracings are monitored continuously. The 30:15 ratio i.e., the ratio of maximum R-R @ $30^{th}$ beat and the minimum R-R at $15^{th}$ beat after standing is calculated. Ziegler et al was the one who redefined 30-15 ratio. According to him longest R-R occurring

between 20-40 and shortest R-R during 5-25 beats is taken and the ratio is calculated.**(75)**

## VALSALVA MANEUVER

During straining phase of valsalva maneuver reflex increase in heart rate and peripheral vasoconstriction occurs first. This is followed by over shoot increase in blood pressure and decrease in heart rate occurs after the strain is released. This reflex response occurs by alternate stimulation of parasympathetic and sympathetic nervous system. In diabetics with autonomic neuropathy the above reflex is deranged. In these patients during the straining phase there is a blunted heart rate and blood pressure response. Also after release of strain there is a slow recovery.

During the procedure of valsalva patient is made to lie supine, connected to ECG recorder. Patient is made to forcibly exhale for 15 seconds with an open glottis against a resistance of 40 mmHg. This produces a sudden but transient augmentation of intra abdominal and intra thoracic pressures.

Patients with lens dislocation, proliferative diabetic retinopathy have a risk of intra ocular hemorrhage.

There are 4 phases in valsalva **(76)**

| | **Response** | **Systolic BP** | **Pulse rate** |
|---|---|---|---|
| Phase I | Onset of strain | Increase | Stable |
| Phase II | Continued strain | Decrease | Increase |
| Phase III | Release | Decrease | Stable |
| Phase IV | Recovery | Increase | Decrease |

Stage I and III are short transient phases.

Stage II and IV are significant phases.

Stage I: with the initial straining the intra thoracic pressure increases squeezing the blood from pulmonary circulation into left atrium. This produces a transient increase in blood pressure.

Stage II: with ongoing strain and raising intra thoracic pressure the venous return to the heart is decreased. This decreases cardiac output producing increased sympathetic activation causing reflex tachycardia and increase in peripheral vascular resistance.

Stage III: With the release of strain the inflow of blood into pulmonary circulation increases but the outflow of blood from left ventricle is also decreased so there is a transient decrease in blood pressure.

Stage IV: recover from strain augments the venous return further producing an increase in blood pressure which reflexly stimulates the baro receptors via vagus producing a fall in heart rate.

Valsalva rate is calculated as the ratio of maximum R-R interval after the straining which reflects the reflex bradycardia to minimum R-R interval during the straining which reflects the reflex tachycardia response.

Valsalva maneuver is the single best method for longitudinal monitoring of the progression of autonomic dysreflexia. In diabetics as it assesses both sympathetic and parasympathetic nerve functions simultaneously.

HRV test performance- summary **(84)**

| | **E:I ratio** | **Valsalva ratio** | **30:15 ratio** |
|---|---|---|---|
| Sensitivity | 0.93 | 0.98 | 0.93 |
| Specificity | 0.93 | 0.91 | 0.93 |
| Positive predictive value | 0.93 | 0.91 | 0.92 |
| Positive predictive value | 0.94 | 0.98 | 0.93 |

## ASSESSMENT OF SYMPATHETIC FUNCTION

## SYSTOLIC BLOOD PRESSURE RESPONSE TO STANDING

In healthy individuals, there is a peripheral pooling of blood in lower limb vessels producing a decreased venous return and cardiac output. This produces a decrease in cardiac output and fall in blood pressure. This stimulates baroreceptors via sympathetics producing a reflex raise in heart rate and peripheral vasoconstriction.reduction in systolic BP is less than 10mmHg in 30sec in normal persons.

In diabetics with autonomic dysreflexia, the compensatory mechanism mediated by baroreceptor stimulation is affected producing a excess fall in systolic BP. Orthostatic response is considered abnormal when systolic BP reduces more than 30 mmHg or diastolic BP reduces more than 10 mmHg within 2 min of standing from supine posture.**(85)**

American Academy of Neurology has redefined orthostatic hypotension as a reduction of systolic BP of more than 20mmHg or diastolic BP of more than 10mmHg associated with symptomatology.**(86)**

**Tilt table testing**

Another standardised method of assessing postural fall in BP is passive head tilting. This is a better method as it is not associated with contraction of lower limb muscles and peripheral pooling of blood.

The patient is made to lie supine in a tilt table and head is passively tilted to 60 degree. This tilt is maintained for 10-60 min or until he develops postural symptoms. Just as in standing response, compensatory mechanisms gets activated and a reflex raise in heart rate and BP fall as outlined before is the response .

**BLOOD PRESSURE RESPONSE TO SUSTAINED HAND GRIP**

By using a hand grip dynamometer, a handgrip that is about 30% of maximum isometric voluntary contraction is maintained for 5 min. diastolic BP before the start of the procedure and just before the release of hand grip is measured. The difference between the two is calculated.

This reflex is mediated by sympathetic system.

A increase in diastolic BP of more than 16 mmHg is normal. An increase of less than 10mmHg is considered abnormal response.

**Frequency domain analysis**

The above methods described for HRV assessment falls under the category of time domain analysis. HRV can also be analysed by power spectral analysis of R-R sequences for a short period or on a 24 hour ECG. This is called frequency domain analysis. The advantage in this method is it needs minimum patient participation as against the previous conventional methods. Heart rate variation in various frequency is analysed. The power spectrum bands of heart rate is divided into two frequency bands.

a. Low frequency band – 0.04-0.15Hz - this is influenced by sympathetic and parasympathetic activity.

b. High frequency band – 0.15-0.4Hz - this is influenced by parasympathetic activity

Various studies have analysed the time domain and frequency domain analysis and have documented a strong association between the two methods by Freeman et al and Howorka et al.**(77,78)**

In Spectral analysis, succeeding sequence of R-R intervals are decomposed. By various mathematical calculations sinusoidal functions of various amplitudes and frequencies are calculated and their

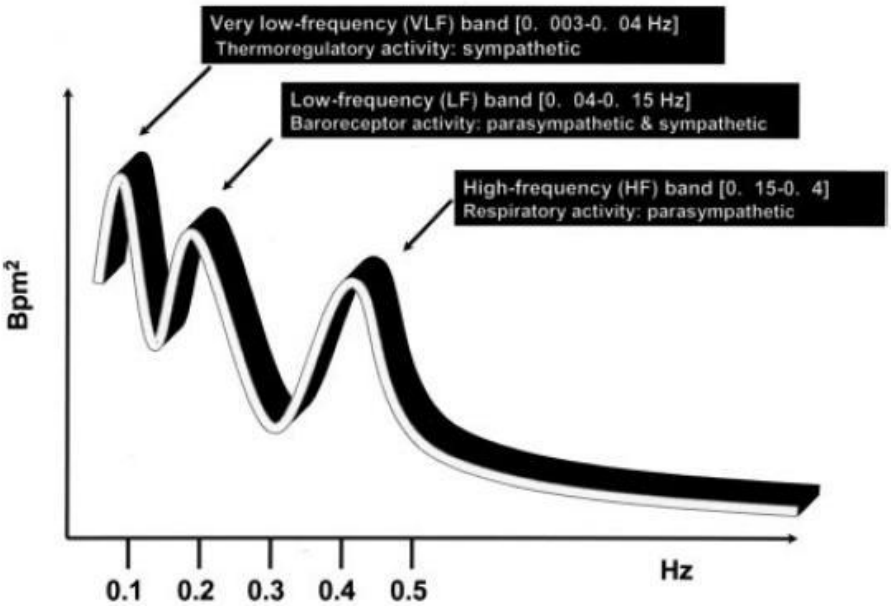
summation is computed. The power spectrum of HRV is obtained which reflects amplitudes of heart rate variations at different frequencies studied.

HRV power spectrum shows three peaks :

1. Very low frequency (less than 0.04Hz)- reflects fluctuation in vasomotor tone – mediated by sympathetic

2. Low frequency zone(0.1 Hz)- represents waves produced by baroreceptor reflex –mediated by both parasympathetic and sympathetic

3. High frequency zone(0.25Hz)- reflects respiratory activity- mediated by parasympathetic system.




R-R intervals.

Sensitive HRV index in diabetic patients for assessing autonomic dysfunction is spectral analysis in low frequency band. Among Ewings battery of tests, HRV to deep breathing, valsalva and 30:15 ratio to standing are sensitive indicators.

Spectral analysis can be used in analysing a 24 hour HRV. In normal individuals low frequency power spectrum mediated by sympathetic predominates during the day and a predominance of high frequency component in the night as it is mediated by vagus.

In diabetics with autonomic dysfunction, this circadian variation is lost. Also they display a decrease in absolute values of both high and low frequency oscillations. Earliest indicator of CAN is decrease in the nocturnal increase of vagal dominated high frequency band.

**EWINGS BATTERY OF TEST – INTERPRETATION**

| **TEST** | **normal** | **Borderline** | **abnormal** |
|---|---|---|---|
| Parasympathetic function | | | |
| Valsalva ratio | >=1.21 | 1.11- 1.20 | <= 1.10 |
| E:I ratio | >=15 | 11-14 | <=10 |
| 30:15 ratio | >=1.04 | 1.01-1.03 | <=1 |
| Sympathetic function | | | |
| Systolic BP fall on standing | <=10 mmHg | 11-29 | >=30mmHg |
| Diastolic BP increase to sustained hand grip | >=16mmHg | 11-15 | <=10mmHg |

**Categories**

I . normal – all test normal or 1parasympathetic test is borderline

II. early- one of the 3 parasympathetic test abnormal or 2 test borderline

III. definite – 2 or more parasympathetic test abnormal

IV. severe - 2 or more parasympathetic test abnormal + one of the sympathetic test abnormal

V. atypical – not fitting into any of the above pattern

**OTHER TESTS OF CAN**

**Spontaneous Baroreflex Testing**

Based on servo plethismomanometry measures this technique beat to beat blood pressure. By this technique neural modulation of sinus node by baroreceptor reflex mechanism is measured.

**Cardiac Radionuclide Imaging**

Radio nucleotide scan uses two norepinephrine analogues

a. MIBG

b. hydroxyephedrine(HED)

MIBG uptake by the myocardium is reduced in patients with CAN. More sensitive method than conventional autonomic reflex testing. The uptake defects in early CAN occurs mostly in left ventricular infero posterior segments.

HED uptake and retention is also reduced in diabetic patients with CAN. In advanced CAN there is a heterogenous retention of HED by the myocardium. Proximal segments of myocardium shows excess retention whereas distal segments shows attenuation. This myocardial dysinnervation – proximal hyperinnervation and distal denervation produces highly electrically unstable myocardium predisposing to arrhythmias.

**MICRO NEUROGRAPHY**

Electrical activity produced by sympathetic nerves innervating peroneal, tibial or radial muscle is recorded and the sympathetic burst is mapped. This sympathetic neurogram produces a characteristic shape which is analysed. Automated sympathetic neurograms assessing beat to beat variations are available.

## CURRENT GUIDELINES FOR CAN TESTING

San Antonio Conference held 1998 and 1992 jointly with ADA and AAN has published a consensus statement regarding autonomic testing in diabetes. The following test are recommended:

For parasympathetic function – heart rate response to

1. deep breathing
2. standing
3. Valsalva maneuver

Sympathetic function testing recommended

Blood pressure response

1. To standing or passive tilting
2. To sustained hand grip

The consensus panel further staged cardiac dysreflexia as follows

1. Early stage: Abnormal heart rate variation to deep breathing alone
2. Intermediate stage: Abnormal valsalva response
3. Severe: Presence of orthostatic hypotension

**Candidates to be screened for CAN - ADA recommendations**

1. All type 2 diabetics at diagnosis and if normal to be screened annually

2. All type 1 diabetics at 5 years after diagnosis and annually thereafter

**Safety of the testing procedure**

Some procedures carry a small theoretical risk. Valsalva increases intra ocular intra thoracic and intracranial pressures and has a small risk on intra ocular hemorrhage in preoliferative diabetic retinopathy and lens dislocation.

DCCT has evaluated 1441 type 1 diabetic patients over 6.5 years with cardiac autonomic function testing without any adverse complications **(79)**

These test when used by properly trained individual is safe and effective.

## MANAGEMENT OF CARDIAC AUTONOMIC DYSREFLEXIA:

### 1. Aid Tight Glycemic Control

Long term poor blood sugar control is the prime risk factor which increases the incidence and progression of cardiac autonomic neuropathy. Mustonen et al documented the association between poor glycemic control and progression of autonomic dysfunction in a 4 year follow up study conducted in a type 2 diabetics**(80)**

DCCT has showed that type 1 diabetics with intensive blood sugar control, has less incidence in the development of abnormal HRV.

Intensive insulin therapy has been effective in preventing the complications in both type 1 and type 2 diabetics.

Delay in treatment of diabetes worsens the autonomic neuropathy.

Tight blood sugar control produces stabilization and prevents further worsening of neuropathy but reversal is less likely.

Hypoglycemic unawareness is more among the individuals with cardiac autonomic neuropathy which warrants regular, more vigilant glycemic monitoring.

## 2. To Initiate Treatment For CAN

Early identification of autonomic dysreflexia in diabetics helps in early initiation of

a. Pharmacological and non pharmacological treatment for BP and dyslipidemia

b. ACE and aspirin prophylaxis

c. Cessation of alcohol and tobacco intake

d. Good nutrition

e. Antioxidants like alpha lipoic acid has promising results in slowing the progression in some studies.Vitamin has also shown some improvement but needs further testing

f. Cardioselective beta blockers by antagonizing sympathetic activity has shown to improve parasympathetic tone. Metaprolol given in type I diabetics has shown improved autonomic function

g. Aldose redutase inhibitors eg., sorbinil and eparlestat have demonstrated improved MIBG uptake in patients with mild CAN. It has no role in advanced disease.

### 3. To Recommend Desired Adherance to Diet And Exercise Regimen

Recently a small study report has shown not only diabetes also prediabetes is associated with diabetic neuropathy

Preventive measures, lifestyle modifications, regular exercise has a definite role in the prevention of micro and macro vascular complications.

CAN testing would enable the physician to explain and intensify non pharmacological therapies among diabetics.

CAN testing also enable physician for a proper exercise regimen that would suit the patient.

### 4. Anaesthetic Implications of CAN Testing

Preoperative cardiovascular autonomic testing in diabetics enables the anaesthesiologist to fore see the intra operative complications especially during general anaesthesia as these patients have a increased fall of heart rate and blood pressure during induction of anaesthesia.

Also these patients have reduced ventilatory drive during the post operative period. Also the need for vasopressors is more in these patients with significant cardiac autonomic neuropathy.

**5. Treatment for Orthostatic Symptoms**

**A. Non Pharmacological Measures:**

1. to increase the intake of water
2. lower extremity elastic stockings
3. frequent small feeds to prevent post prandial hypotension
4. avoid straining as raised intra abdominal and intrathoracic pressures impedes venous return
5. physical maneuvers like squatting, leg crossing increased cardiac filling and stroke volume
6. checkout for drugs that aggravate hypotension eg., TCAs, phenothiazides

**B. Pharmocological Measures**

1. Midodrine

- selective, peripheral A 1 receptor agonist

- only agent approved by FDA for the treatment of orthostatic hypotension
- dose 2.5 – 10 mg three times a day
- fewer CNS side effects as it does not cross the blood brain barrier
- adverse effects- pruritis, paresthesias, urinary retention, piloerection, supine hypertension **(81)**

2. Fludrocortisone acetate

- synthetic mineralocorticoid
- long plasma half life
- lncreases the sensitivity of the blood vessels to circulating catecholamines
- increases plasma expansion
- dose 0.05 mg @ bed time titrate slowly to a maximum dose of 0.2 mg/day
- adverse effects –supine hypertension , hypokalemia, fluid retention, hypomagnesemia, congestive cardiac failure **(82)**

3. Erythropoietin

- increases RBC mass, blood volume, mediates neuro humoral effects on blood vessel wall and regulates the vascular tone by mediating interaction of haemoglobin and nitric oxide.

- dose 25- 75 units per kg body wt three times a week sc/iv until patient achieves normal haematocrit. Maintain on a low dose of 25 units/kg thrice a week **(82)**

4. Nonselective B blockers

- these drugs blocks the B2 receptors of blood vessel which mediate vaso dilatation and thereby facilitates unopposed alpha receptor mediator vasoconstriction

- limited role for these drugs **(82)**

5. Clonidine

- Alpha 2 blocker

- central sympatholytic activity

- in patients with severe CAN the central sympathetic efferent activation is blunted and clonidine produces

increase in venous return without affecting peripheral vascular resistance

– limited use due to serious adverse effects **(82)**

6. Somatostatin analogues

- these drugs inhibit vasoactive peptides released from GIT, increases splanchnic vasoconstriction , venous return and cardiac output

- dose 25-200 micrograms /day

- development of severe hypertension precludes its use

7. Pyridostigmine bromide

- cholinesterase inhibitor

- increases ganglionic transmission without affecting supine hypertension **(83)**

8. Fluoxetine

- SSRI has shown improvement in symptoms in patients with Parkinson disease

**Ansiscope (85)**


Ansiscope is an electronic instrument which measure sympathetic and para sympathetic activity with each heart beat. Dysautonomia is defined by lack of concordance between the parasympathetic-sympathetic system. The measurement is made in 10- 15 minutes. The patient is made to lie in the supine position comfortably. The electrodes are connected to the patient and the individual is made to lie in rest.

The ansiscope counts 571 R-R intervals. For this a good ECG signal must be obtained. The R of the QRS peak must be well defined.

The ansiscope measures the coupling between the autonomic nervous system. It measures the amount of time the two system not working in concordance with in the count of 571 R-R interval and this

sympatho vagal imbalance is given as percentage value which implies the proportion of time the two systems are decoupled.

The heart rate variability is the underlying mechanism which is measured. It is a mathematical instrument which works under the physical principle of scale covariance law.

At the end of measurement the ansiscope displays the following two information

A. the percentage of autonomic dysfunction

B. patient classification as healthy , early , late , advanced and most advanced based on the percentage of dysautonomia

**Advantages**

1. quick measure of cardiac dysautonomia
2. time advantage
3. non invasive
4. patient friendly
5. does not involve patient effort/ maneuver

6. does not involve tedious calculations as conventional autonomic scoring

7. reproducible

8. no recurring expenditure

9. helps in the monitoring of therapy

10. no other device available till now

11. portable

**Disadvantages**

1. initial expenditure

2. not standardized

# MATERIALS AND METHODS

## PLACE OF STUDY

Department of General Medicine – OP and IP patients, Govt Stanley Medical College and Hospital, Chennai.

## DURATION

FEB 2013 – DEC 2013

## STUDY DESIGN

PROSPECTIVE OBSERVATIONAL STUDY

## PATIENT SELECTION

TYPE 2 DIABETIC PATIENTS

## EXCLUSION CRITERIA

Patients with the following are excluded from the study

1. End organ damage in the form of coronary artery disease,CCF,
2. Patients on anti depressants, sympathetic blockers, vasodilators, anti histamines, diuretics, aspirin

3. Age more than 70

4. Proliferative diabetic retinopathy

5. Alcoholics

## METHODOLOGY

Patients with Type 2 diabetes in both OP AND IP basis from FEB 2013 to DEC 2014 were included in the study. Patients were subjected to symptom analysis, clinical examination and laboratory investigations.

Eligible cohorts were subjected to standard autonomic testing and testing with ANSiscope.

Standard autonomic testing includes

Assessing heart rate variability with

1. deep breathing
2. valsalva
3. supine to standing position

Assessing blood pressure variability with

1. supine to standing

**Procedure**

Resting ECG was taken for all the patients. Individuals in the study group were subjected to ECG recordings. Preferred lead is lead II.

Subjects were made to lie supine comfortably. Then they were asked to take deep breathe evenly at the rate of 6 breaths per minute i.e., 5 seconds for inspiration and 5 seconds for expiration. A continuous ECG was recorded for one minute. The maximum and minimum R-R interval during the respiratory cycle was calculated and converted to beats per minute. The difference between the two and heart rate variation of less than 10 beats per minute was taken as abnormal. Then the patient was allowed to lie quietly for another 5 minutes. The patient was made to exhale forcibly into the mouth piece of manometer sustaining a pressure of 40 mmHg for about 15 seconds and the ECG was recorded continuously. The patient was made to stop the maneuver and the ECG was further recorded post maneuver. The ratio of shortest R-R interval during the maneuver and the longest R-R post valsalva was calculated. A ratio less than 1.10 was considered abnormal. Again the patient was made to lie supine quietly. After about 5 minute with continuous monitoring the patient was made to stand. The R-R internal

at $15^{th}$beat and $30^{th}$ beat was calculated. The 30:15 ratio of less than 1.00 was considered abnormal.

For the assessment of the sympathetic function, patient was made to lie down and his BP recorded. Then he was made to stand up and again BP measurement was made 2 minutes after standing. A fall of systolic Blood Pressure more than 30 mmHg was considered abnormal. Based on the above standard testing patients with 2 or more abnormal test were classified as definite, one of the three heart rate variability test abnormal were classified as early. When individuals with parasympathetic dysfunction along with significant BP fall were classified as severe CAN as per Ewings et al.

For testing of patients with ansiscope, patients were instructed to lie supine comfortably. The electrodes were connected and after obtaining good ECG signal the test was commenced. At the end of count of 571 R-R intervals the instrument display the presence/absence of CAN and the severity.

# OBSERVATIONS AND DATA ANALYSIS

## 1. SEX DISTRIBUTION

| Sex | Frequency | % of Study Group |
|---|---|---|
| MALE | 30 | 35.7 |
| FEMALE | 54 | 64.3 |
| TOTAL | 84 | 100 |

## 2. CAN POSITIVITY

| CAN | Ansiscope | | Conventional | |
|---|---|---|---|---|
| | Frequency | Percentage | Frequency | Percentage |
| Yes | 70 | 83.3 | 75 | 89.3 |
| No | 14 | 16.7 | 9 | 10.7 |
| TOTAL | 84 | 100 | 84 | 100 |

## 3. SEVERITY OF CAN

| | Ansiscope | | Conventional | |
|---|---|---|---|---|
| | **Frequency** | **Percentage** | **Frequency** | **Percentage** |
| EARLY | 9 | 12.8 | 19 | 25.0 |
| LATE | 47 | 67.1 | 53 | 69.7 |
| ADVANCED | 14 | 20 | 4 | 5.26 |
| TOTAL | 70 | 100 | 76 | 100 |

## 4. VALSALVA RATIO

| | **Frequency** | **Percentage** |
|---|---|---|
| NORMAL | 16 | 19 |
| BORDERLINE | 45 | 53.6 |
| ABNORMAL | 23 | 27.4 |
| TOTAL | 84 | 100 |

## 5. E:I RATIO

| | **Frequency** | **Percentage** |
|---|---|---|
| NORMAL | 9 | 10.7 |
| BORDERLINE | 15 | 17.9 |
| ABNORMAL | 60 | 71.4 |
| TOTAL | 84 | 100 |

## 6. 30:15 RATIO

| | Frequency | Percentage |
|---|---|---|
| NORMAL | 11 | 13.1 |
| BORDERLINE | 20 | 23.8 |
| ABNORMAL | 53 | 63.1 |
| TOTAL | 84 | 100 |

## 7. ORTHOSTATIC HYPOTENSION

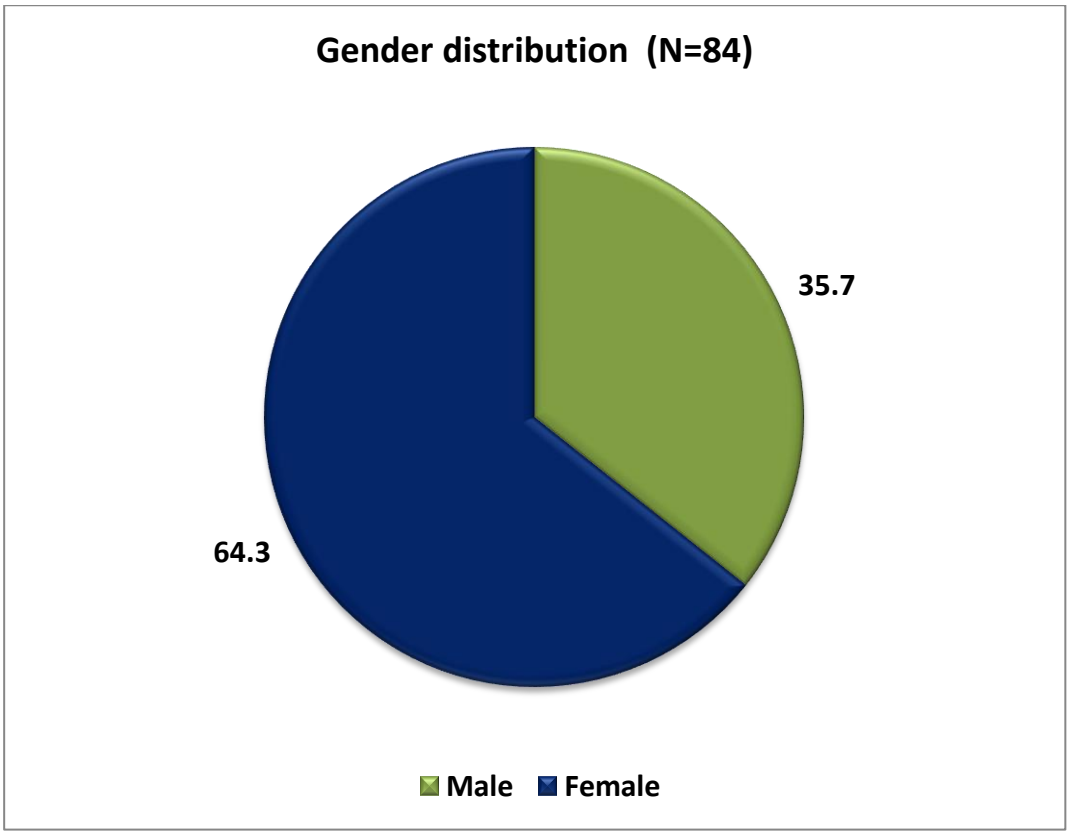
| | Frequency | Percentage |
|---|---|---|
| NORMAL | 59 | 70.2 |
| BORDERLINE | 21 | 25.0 |
| ABNORMAL | 4 | 4.8 |
| TOTAL | 84 | 100 |

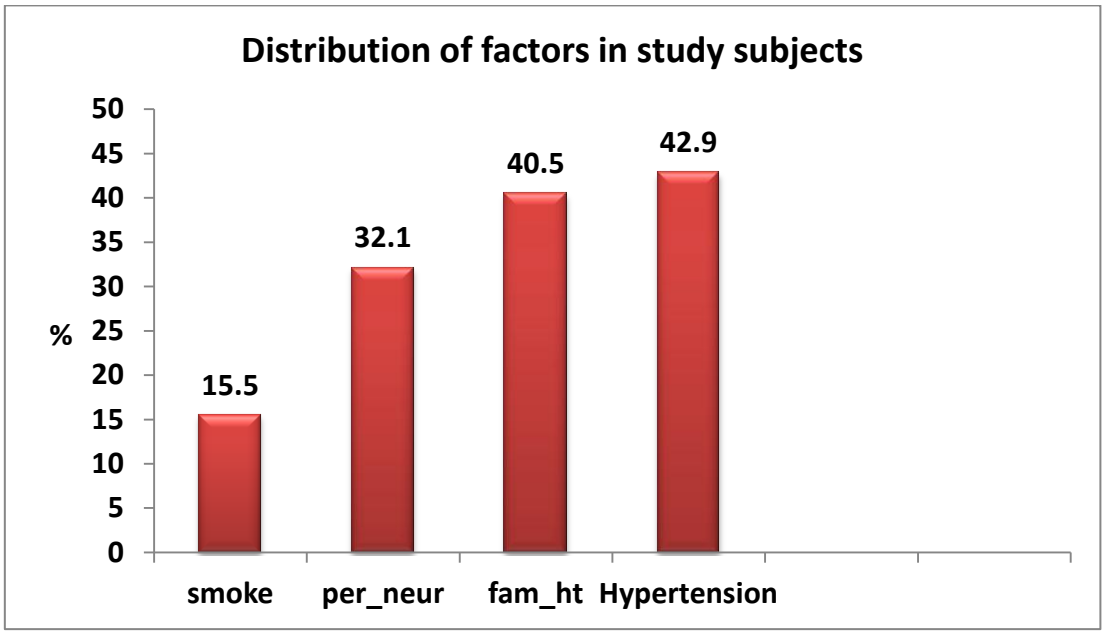
## 8. SENSITIVITY AND SPECIFICITY OF THE HRV TEST

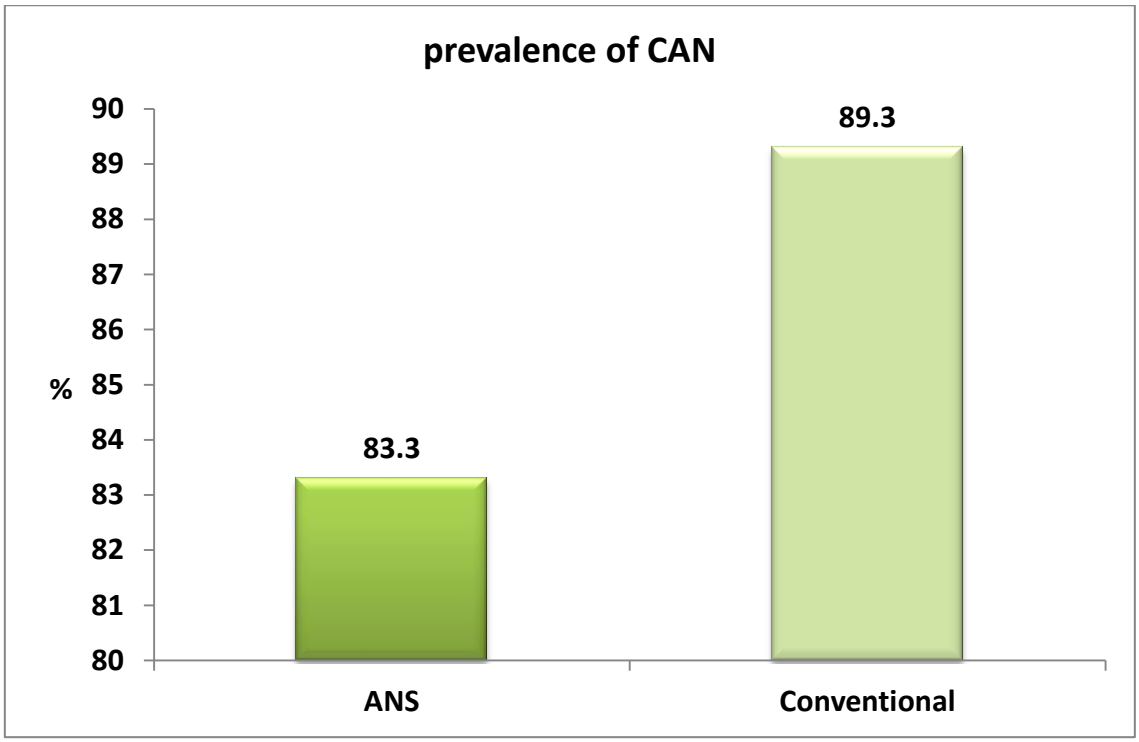
| Test | Sensitivity (%) | Specificity (%) |
|---|---|---|
| VALSALVA RATIO | 86.7 | 66.7 |
| E:I RATIO | 92 | 33.3 |
| 30:15 RATIO | 92 | 55.6 |

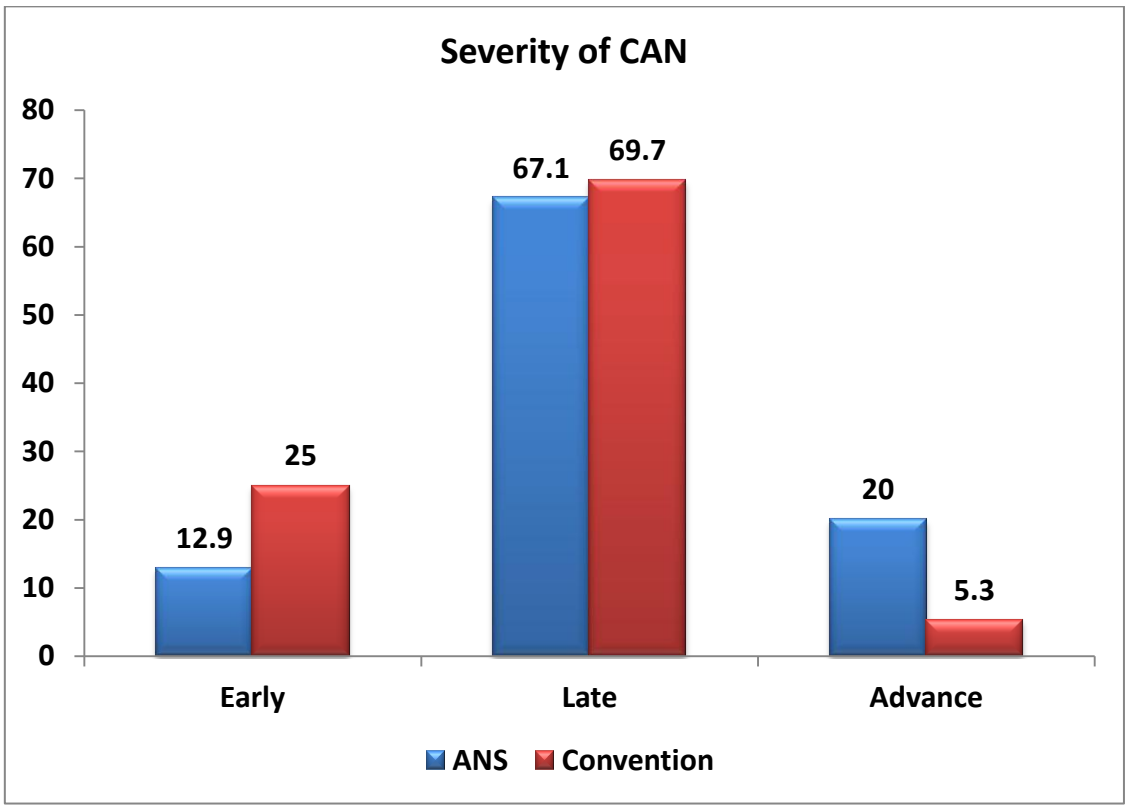
# 9. ASSOCIATION OF VARIOUS PARAMETERS WITH CAN

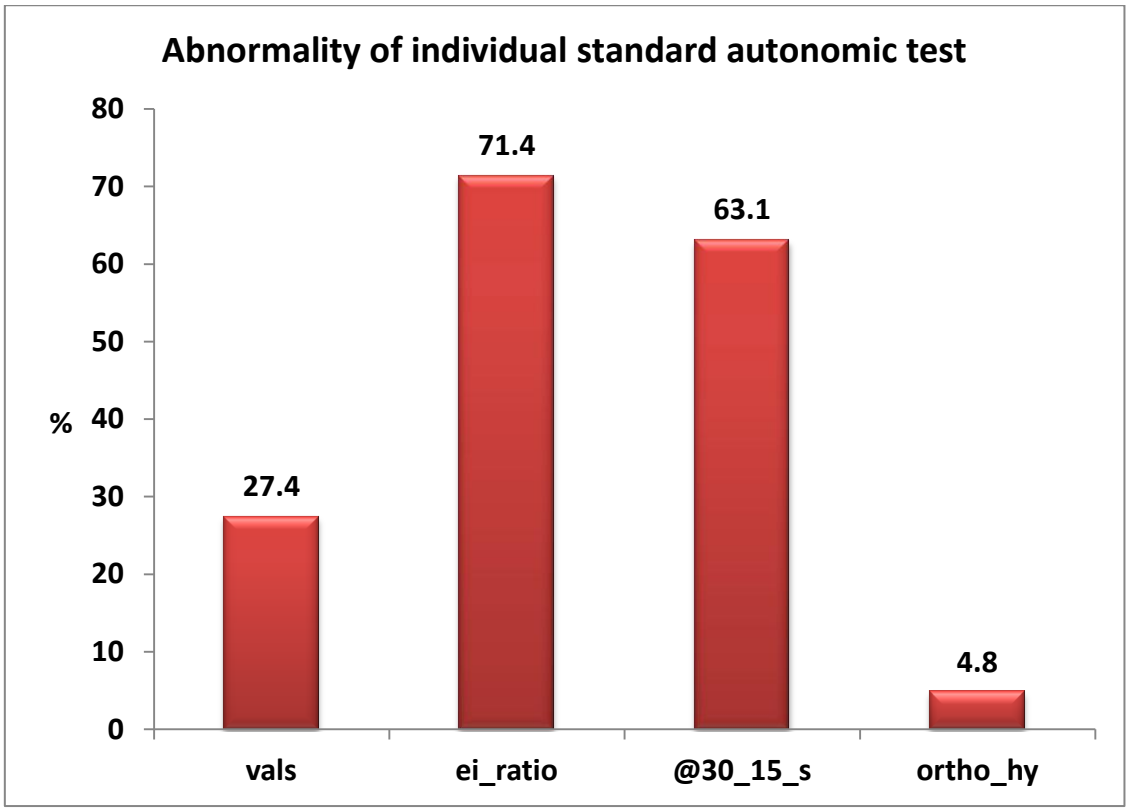
| Parameter | % of subjects | Prevalence of CAN | | p Value | |
|---|---|---|---|---|---|
| | | Conven-tional | Ansiscope | Conven-tional | Ansiscope |
| SMOKERS | 15.5% | 100% | 92.3% | 0.384 | 0.58 |
| HYPERTENSION | 42.9% | 91.9% | 86.1% | 0.799 | 0.761 |
| PERIPHERAL NEUROPATHY | 32.1% | 96.3% | 92.6% | 0.293 | 0.210 |
| DURATION OF DIABETES | | | | | |
| a. at diagnosis | 19% | 81.2% | 68.8% | 0.344 | 0.106 |
| b.1-5 years | 59.5% | 88% | 82% | | |
| c.>5 years | 21.5% | 100% | 100% | | |
| UNAWARE | 75% | 93.7% | 85.7% | 0.039 | 0.049 |
| POOR SUGAR CONTROL | 33.33% | 100% | 96.4% | 0.026 | 0.029 |

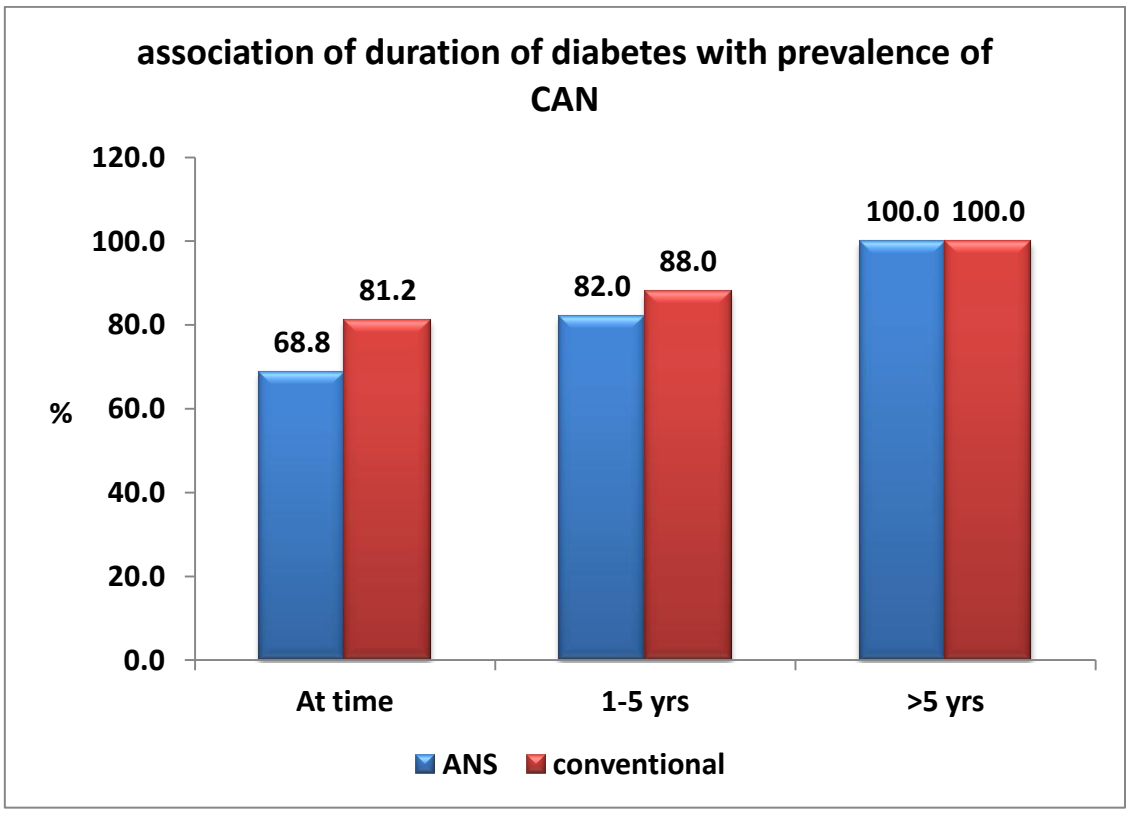

Gender distribution (N=84)
35.7
64.3
Male
Female

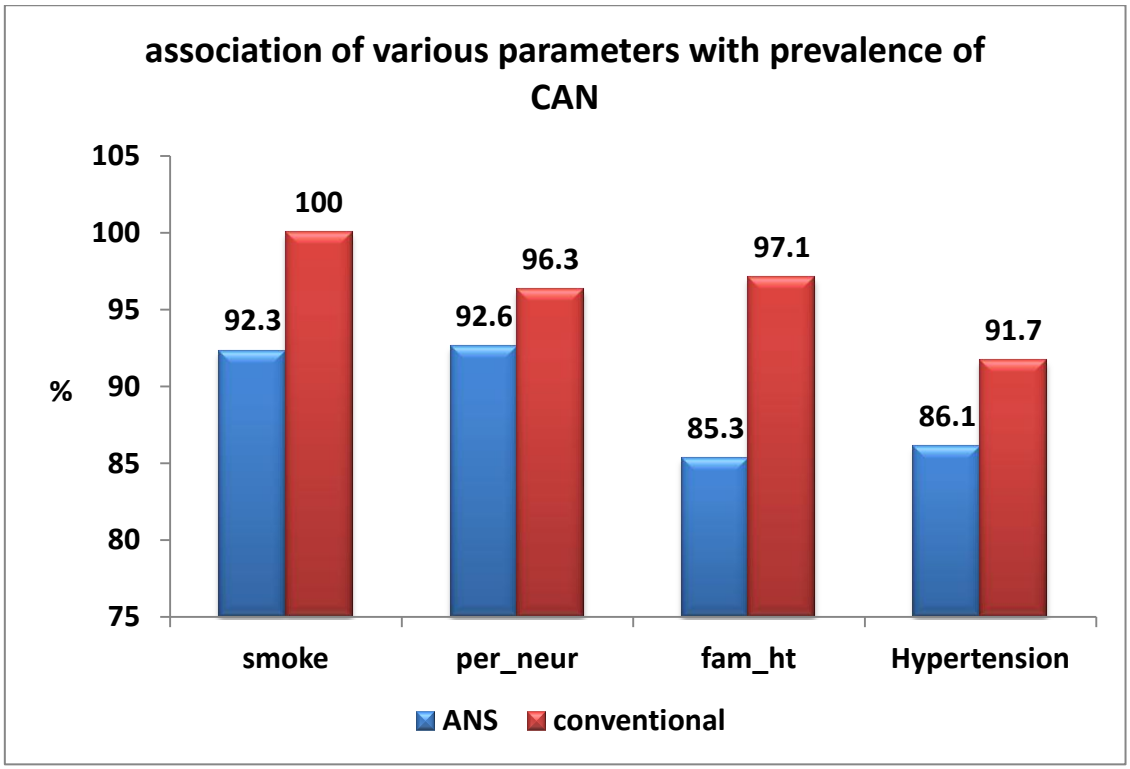

Distribution of factors in study subjects
%
50
45
40
35
30
25
20
15
10
5
0
15.5
32.1
40.5
42.9
smoke
per_neur
fam_ht
Hypertension

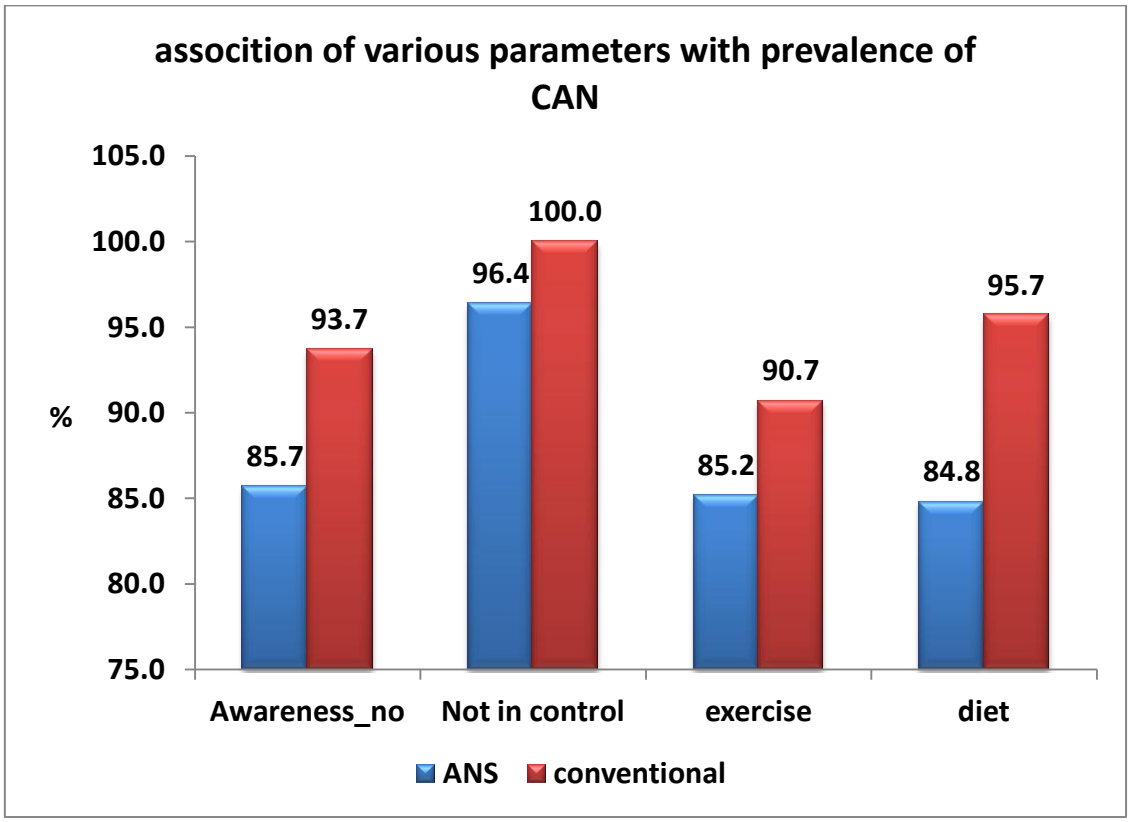

prevalence of CAN
90
89
88
87
86
%
85
84
83
82
81
80
83.3
89.3
ANS
Conventional


Severity of CAN
80
70
60
50
40
30
20
10
0
12.9
25
67.1
69.7
20
5.3
Early
Late
Advance
ANS
Convention


Abnormality of individual standard autonomic test
80
70
60
50
% 40
30
20
10
0
27.4
71.4
63.1
4.8
vals
ei_ratio
@30_15_s
ortho_hy


association of duration of diabetes with prevalence of CAN
120.0
100.0
80.0
% 60.0
40.0
20.0
0.0
68.8
81.2
82.0
88.0
100.0
100.0
At time
1-5 yrs
>5 yrs
ANS
conventional


association of various parameters with prevalence of CAN
105
100
95
90
85
80
75
%
92.3
100
92.6
96.3
85.3
97.1
86.1
91.7
smoke
per_neur
fam_ht
Hypertension
ANS
conventional


association of various parameters with prevalence of CAN
105.0
100.0
95.0
90.0
85.0
80.0
75.0
%
85.7
93.7
96.4
100.0
85.2
90.7
84.8
95.7
Awareness_no
Not in control
exercise
diet
ANS
conventional

# RESULTS

1. Among the total 84 individuals studied 64.3 % were females and 35.7 % were males.

2. A total of 15.5%(13 persons) were smokers and among them 92.3%(12 persons) and about 100% (13 people) were found to have cardiac autonomic neuropathy by ansiscope and conventional methods respectively.

3. 27 subjects i.e. 32% were found to have peripheral neuropathy by clinical testing and among them 92.6% (25 persons) tested positive for autonomic neuropathy by ansiscope and 96.3% (26 persons ) by conventional method

4. 36 subjects (42.9%) of the study population were hypertensive and of them 31 people(86.1%) and 33 people (91.7%) tested positive for autonomic dysfunction by ansiscope and conventional method respectively.

5. Of the 84 study subjects 63 (75%) people were not aware of the complications related to diabetes. In them 54 subjects(85.7% ) and 59 subjects(93.7%) tested positive for cardiac autonomic

neuropathy by ansiscope and conventional methods respectively. This association is found to be statistically significant.

6. A total of 16 subjects (19%) were examined at diagnosis. Among them 11 individuals 68.8% were CAN positive by ansiscope and 81.2 % (13 subjects) by conventional method.

7. Of the 84 individuals 50 individuals were diabetic for a duration 1-5 years. Among them 82% (41 individuals) and 88%(44 subjects) tested positive for autonomic dysfunction by ansiscope and conventional method respectively.

8. Of the 18 subjects who were diabetic for more than 5 years, were tested 100% positive for autonomic dysfunction by both the methods.

9. 28 individuals had poor glycemic control. All individuals with poor glycemic control tested positive for cardiac autonomic dysfunction by conventional method and 96.4% (27 individuals) tested positive by ansiscope. This association is statistically significant.

10. Of the 84 subjects tested 27.4% (23 individuals) had abnormal valsalva ratio. 71.4% (60 individuals) ha d abnormal inspiratory and expiratory ratio. 63.1% (53 individuals) had abnormal 30:15 ratio. And 4 individuals (4.8%) had significant abnormal orthostatic hypotension.

11. 12.9% of the individuals had tested 'early' dysfunction by ansiscope. 67.1 % had 'late' and 20% were categorized as 'advanced' by ansiscope testing.

12. 25% individuals had 'early',69.7% had 'definite' and 5.3% had 'advanced' cardiac autonomic dysfunction.

13. Sensitivity and specifity of the individual test are as follows

Valsalva - 86.7% and 66.7%

E: I ratio - 92% and 33.3%

30:15 ratio - 92% and 55.6% respectively.

# DISCUSSION

This study was done to assess the prevalence of cardiac autonomic dysfunction in Type 2 diabetics by ansiscope and conventional methods which assess the heart rate variability.

The prevalence rate was 83.3% and 89.3% by ansiscope and conventional methods respectively.

Our study included diabetics of less than one year as ‘at diagnosis’.

‘At diagnosis’ 68.8% were CAN positive by ansiscope and 81.2 % by conventional method. In individuals with a duration 1-5 years, 82% and 88% tested positive for autonomic dysfunction by ansiscope and conventional method respectively. Diabetics for more than 5 years, were tested 100% positive for autonomic dysfunction by either of the methods.

Khandellwal E et al has assessed the evidence of CAN using Ewing’s criteria as 79%. Using the same criteria Ramavat manish R et al concluded the prevalence of CAN around 51.9%.

Viveka P Jyotsna et al studied the prevalence of CAN in type 2 individuals at diagnosis and found the rate of cardiac dysfunction as 71% **(86-88).**

In the present study though there is an increased percentage positivity of Cardiac Autonomic Dysfunction in individuals with smoking, peripheral neuropathy, duration of diabetes we did not find any significant association. In our study there is a significant association of CAN positivity in individuals who were unaware of the complications of diabetes.

There is a significant positive association of cardiac autonomic dysreflexia in individuals with poor glycemic control in our study. All individuals with poor glycemic control tested positive for Cardiac Autonomic Dysfunction by conventional method and 96.4% tested positive by ansiscope.

EURO DIAB study has found that the incidence of autonomic neuropathy is associated with poor glycemic control.

STENO TYPE 2 trial has followed up intensively controlled diabetics for 8 years and documented a reduced rate of progression of autonomic neuropathy.

DCCT research group had shown that intensive therapy for diabetics decreases the rate of progression and delays the development of autonomic dysfunction.

In our study we have found the heart rate variation with E:I ratio and 30:15 ratio is 92% and is found more sensitive compared to other methods.

# CONCLUSION

The prevalence of cardiac autonomic neuropathy is extremely high among diabetics as shown in our study. Most diabetic patients have significant autonomic dysreflexia even at diagnosis of diabetes. Cardiac autonomic neuropathy is the single important factor which predicts the 5 year mortality rate among diabetics. Poor blood sugar control is significantly associated with CAN and is the single best factor which determines the rate of progression as cited in our study. Also individuals who are unaware of the complications of diabetes have shown a significant association with autonomic dysreflexia. Early screening, early diagnosis, proper education of patients and strict glycemic control help in the arrest of progression of Cardiac Autonomic Neuropathy in Type 2 diabetic population.

# BIBLIOGRAPHY


1. Ramachandran A high prevalence of diabetes and cardiovascular risk factors associated with urbanization in India. Diabetes Care 2008; 893-898.

2. Prior IA, epidemiology of diabetes in Polynesians and Europeans in Newzealand and Pacific, N Z med J 1966;1966;65:375-383.

3. Ramachandran A, diabetes in Asia , Lancet 2010; 375:408-418, (Unwin N,IDF diabetes atlas 4th edition Brussels).

4. Ramachandran A, Diabetes prevention and control programme in developing countries, oxford univ press : 2011, 603-621.

5. InterAct Consortium. The link between family history and risk of type 2 diabetes is not explained by anthropometric, lifestyle or genetic risk factors: the EPIC-InterAct study. Diabetologia 2013; 56:60.

6. Meigs JB, Cupples LA, Wilson PW. Parental transmission of type 2 diabetes: the Framingham Offspring Study. Diabetes 2000; 49:2201.

7. Shai I, Jiang R, Manson JE, et al. Ethnicity, obesity, and risk of type 2 diabetes in women: a 20-year follow-up study. Diabetes Care 2006; 29:1585.

8. DeFronzo RA, Ferrannini E. Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 1991; 14:173.

9. Reis JP, Loria CM, Sorlie PD, et al. Lifestyle factors and risk for new-onset diabetes: a population-based cohort study. Ann Intern Med 2011; 155:292.

10. Manson JE, Ajani UA, Liu S, et al. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. Am J Med 2000; 109:538.

11. Cappuccio FP, D'Elia L, Strazzullo P, Miller MA. Quantity and quality of sleep and incidence of type 2 diabetes: a systematic review and meta-analysis. Diabetes Care 2010; 33:414.

12. McMullan CJ, Schernhammer ES, Rimm EB, et al. Melatonin secretion and the incidence of type 2 diabetes. JAMA 2013; 309:1388.

13. van Dam RM, Rimm EB, Willett WC, et al. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. Ann Intern Med 2002; 136:201.

14. Stranges S, Marshall JR, Natarajan R, et al. Effects of long-term selenium supplementation on the incidence of type 2 diabetes: a randomized trial. Ann Intern Med 2007; 147:217.

15. Balk EM, Tatsioni A, Lichtenstein AH, et al. Effect of chromium supplementation on glucose metabolism and lipids: a systematic review of randomized controlled trials. Diabetes Care 2007; 30:2154.

16. American Diabetic Association, diabetes care, volume 36, supplement 1, January 2013.

17. The prevalence by staged severity of various types of diabetic neuropathy, retinopathy, and nephropathy in a population-based cohort: The Rochester Diabetic Neuropathy Study. Neurology 1993; 43:817–24.

18. Young MJ, Boulton AJM, MacLeod AF, Williams DRR, Sonksen PH. A multicentre study of the prevalence of diabetic peripheral neuropathy in the United Kingdom hospital clinic population. Diabetologia 1993;36:1–5.

19. Vinik A. Diabetic neuropathy: pathogenesis and therapy. Am J Med 1999;107:17S–26S.

20. Holzer SE, Camerota A, Martens L, Cuerdon T, Crystal-Peters J, Zagari M. Costs and duration of care for lower extremity ulcers in patients with diabetes. Clin Ther 1998;20:169–81.

21. Ziegler D, Dannehl K, Mu¨ hlen H, Spu¨ ler M, Gries FA. Prevalence of cardiovascular autonomic dysfunction assessed by spectral analysis, vector analysis, and standard tests of heart rate variation and blood pressure responses at various stages of diabetic neuropathy. Diabet Med 1992;9:806–814

22. Consensus Statement. Report and recommendations of the San Antonio conference on diabetic neuropathy. American Diabetes Association American Academy of Neurology.Diabetes Care 1988;11:592–7.

23. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. N Engl J Med 1993;329:977–86.

24. Ziegler D, Cicmir I, Mayer P, Wiefels K, Gries FA. Somatic and autonomic nerve function during the first year after diagnosis of type 1 (insulin-dependent) diabetes. Diabetes Res 1988;7:123–7.

25. Bird SJ, Brown MJ. The clinical spectrum of diabetic neuropathy. Semin Neurol 1996;16:115–22.

26. United Kingdom screening test – young MJ, multi centre study of prevalence of diabetic peripheral neuropathy in UK hospital population; Diabetolgia 1993; 36:150.

27. Mayfield JA, Sugarman JR. The use of Semmes-Weinstein monofilament and other threshold tests for preventing foot ulceration and amputation in people with diabetes. J Fam Pract 2000;49:
517–29.

28. Amthor KF et al. The effect of 8 years of strict glycaemic control on peripheral nerve function in IDDM patients: the Oslo Study. Diabetologia 1994;37:579–84

29. McQuay H, Carroll D, Jadad AR, Wiffen P, Moore A. Anticonvulsant drugs for management of pain: a systematic review. BMJ 1995;311:1047–52.

30. [133] Gorson KC, Schott C, Herman R, Ropper AH, Rand WM. Gabapentin in the treatment of painful diabetic neuropathy: a placebo controlled, double blind, crossover trial. J Neurol Neurosurg Psychiatry 1999;66:251–2.

31. Greene DA, Arezzo JC, Brown MB. Effect of aldose reductase inhibition on nerve conduction and morphometry in diabetic neuropathy. Zenarestat Study Group. Neurology 1999;53:580–91.

32. Ziegler D, Gries FA. Alpha-lipoic acid in the treatment of diabetic peripheral and cardiac autonomic neuropathy. Diabetes 1997;46(Suppl 2):S62–6.

33. Young RJ , variable relationship between peripheral somatic and autonomic neuropathy in patients with different syndromes of diabetes polyneuropathy . diabetes 1986 feb ;35(2): 192-7.

34. Llunch L, cardiovascular autonomic neuropathy in type 1 diabetic patients with and without peripheral neuropathy. Diabetes Res Clin Pract. 1998 Oct; 42(1): 35-40.

35. Rajiv A. Gandhi , painful diabetic neuropathy is associated with greater autonomic dysfunction than painless diabetic neuropathy : Diabetes care 33: 1585-1590, 2010.

36. Austin ma, small, dense LDL, insulin resistance syndrome and non-insulin dependent diabetes. Curr Opin Lipidol. 1996;7:167-171.

37. .Nelson RG, prediabetic blood pressure predicts urinary albumin excretion after the onset of type 2 (NIDDM)Diabetes mellitus in pima Indians. Diabetolgia. 1993;306:345-347.

38. Edelson GW, Insulin resistence in hypertension: a focused review. Am J Med Sci.1993;306:345-347.

39. ReavenGM, Hypertension and associated metabolic abnormality:the role of insulin resistence and sympathoadrenal system. N Engl J Med .1996;334:374-381.

40. .Byberg L, plasminogen activator inhibitor-1 activity is independently related to both insulin sensitivity and serum triglycerarides in 70 year old men. Arterioscler Thromb Vasc Biol. 1998;18:258-264.

41. Boudina S, Diabetic cardiomyopathy Revisited. Circulation, 2007;115(25):3213-3223.

42. Stamler J,diabetes and 12 year cardiovascular mortality in men screened in multiple risk factor intervention Trial, diabetes care 1993; 16:434-444.

43. Grundy S.M, obesity, metabolic syndrome and cardiovascular disease.J Clin Endocrine Metb. 2004;89(6):2595-2600.

44. http://emedicine.medscape.com/article/1923077-overview#aw2aab6b3

45. Cardiac autonomic neuropathy in diabetes – a clinical perspective diabetes care vol 33 no.2 feb 2010 Rodica pop-busui

46. kahn j decreased exercise heart rate in diabetic subjects with CAN diabetes care 9;389 -394 ,1986

47. roy TM Autonomic influence on cardiovascular performance in diabetic subjects AM J MED 87;382-388,1989

48. Burgos LG increased intraoperative cardio vascular morbidity in diabetics with autonomic neuropathy. Anaesthesiology 70; 591 - 597,1989

49. kitamura A; patients with diabetic neuropathy are at risk of greater intra operative reduction of core temperature – anesthesiology 92 ; 1311- 1318,2000

50. sobotka PA; impaired hypoxic ventilator drive in diabetic patients with autonomic neuropathy JClin endocrinal metab 62; 658-663,1986

51. Ambeptitiyia g. ;exertional myocardial ischemia in diabetes: a quantitative analysis of angina percepyion threshold and the influence of autonomic fucction, j Am Coll Cardiol 15:72 – 77, 1990

52. vinik AI , diabetic autonomic neuropathy. Diabetes care 2003;26:1553- 1559

53. young LH , cardiac outcomes after screening for asymptomatic coronary disease in patients with type 2 diabetes ;DIAD study:JAMA2009;301: 1547- 1555.

54. Pop – Busui R , SYMPATHETIc DYSFUNCTION IN TYPE 1 DIABETICS :ASSOCIATION WITH IMPAIRED MYOCARDIAL BLOOD FLOW RESERVE AND DIASTOLIC DYSFUNCTION . J Am Coll Cardiol 2004; 44: 2368 – 2374.

55. O ‘ brien IA, influence of autonomic neuropathy on mortality in IDDM. J Med 79 :495- 502 , 1991.

56. O‘ brien IA, influence of autonomic neuropathy on mortality in IDDM. J Med 79 :495- 502 , 1991.

57. Orchard TJ, why does diabetic autonomic neuropathy predict IDDM mortality , an analysis from the Pittsburgh epidimology of diabetics complications study. Diabetes Res Clin Pract 34 S165- S 171, 1996.

58. Fava S, factors that influence the outcome in diabetics subjects with MI .diabetec care 16 : 1615 – 1618 , 1993.

59. Katz A, a simple bed side test of 1 min HRV during deep breathing as a prognostic index after MI , Am heart J 138: 32- 38 , 1999.

60. Toyry JP, Autonomic neuropathy predicts the development of stroke in patients with NIDDM. Stroke 27 : 1316 – 1318 , 1996.

61. Ziegler D, diabetic cardiovascular autonomic neuropathy multicentre study group :the epidiomology of diabetic neuropathy. J Diabetic complications 6:49-57, 1992.

62. Ziegler D, diabetic cardiovascular autonomic neuropathy multicentre study group :the epidiomology of diabetic neuropathy. J Diabetic complications 6:49-57, 1992.

63. Ziegler D: diabetic cardiovqascular autonomic neuropathy :prognosis, diagnosis, and treatment . diabetes Metab review 10 :339- 383, 1994.

64. DCCT research group : effect of intensive diabetes therapy on measures of autonomic nervous system function in diabetes control and complications trial diabetolgia 41:416 – 423, 1998.

65. Sampson MJ, progression of diabetic autonomic neuropathy over a decade of IDDM j Med 75: 635-646, 1990.

66. Oxidative stress and Nrf2 in the pathophysiology of diabetic neuropathy: Old perspective with a new angle Biochemical and Biophysical Research Communications 408 (2011) 1–5.

67. Geeta Negi, Oxidative Stress and Diabetic Complications *Circ Res.* 2010;107:1058-1070.

68. Ferdinando Giacco and Michael Brownlee FREE RADICALS, OXIDATIVE STRESS, AND DISEASES accessed online http://web.mst.edu/~nercal/documents/chem464/lectures/lec01_freeradicals.pdf.

69. Oxidative Stress in the Pathogenesis ofDiabetic Neuropathy Endocrine Reviews 25(4):612–628.

70. Andrea M. Vincent, Role of different molecular pathways in the development of diabetes induced nephopathy – diabetes and metabolism 2013 S 9.

71. Vir Vikram Sharma, Complications: neuropathy, pathogenetic considerations diabetes care vol 15 no.12 dec 1992.

72. Ewing DJ, The value of cardiovascular autonomic function test; 10 years experience in diabetes. Diabetes Care 8;491-498,1985

73. Ziegler, Assessment of cardiovascular autonomic function age related normal ranges reproducibility of spectral analysis, vector analysis and standard test of heart rate variation and blood pressure. Diabet med 9:166- 175, 1992.

74. Sapira JD, the art and science of bed side diagnosis first edition page 444-446 1990.

75. Freeman R,spectral analysis of heart rate in diabetic autonomic neuropathy Arch Neurol 48;185-190,1991.

76. Howorka K,optimal parameters for shortterm heart rate spectrogram for routine evaluation of diabetic cardiovascular autonomic neuropathy J Auton Nerv Syst 69;164-172,1998.

77. DCCT research group – the effect of intensive diabetic therapy on autonomic nervous system functions in diabetes control and complications trial – diabetolgia 41; 416-423, 1998.

78. Mustonen J, changes in autonomic nervous function during 4 year follow up in middle aged diabetic and non diabetic subjects initially free of coronary heart disease J intern Ned 241 :227-235,1997.

79. Vinik AI, diabetic autonomic neuropathy, diabetes care 2003 ; 26;1553-1579.

80. Freeman R treatment of orthostatic hypotension.Semin Neurol 2003 : 23-435-442.

81. Singer W pyridostigmine trial in neurogenic orthostatic hypotension Arch Neural 2006 ,63;513-518.

82. AI vinik and M Risk, diabetes care vol 26 No.5 may 2003.

83. Ewing DJ, Assessment of cardiovascular effects in diabetic autonomic neuropathy and prognostic implications,Ann Inn Med 92: 308-311, 1980.

84. Position paper:orthostatic hypotension, multisystem atrophy and pure autonomic failure j auton Nerv Syst 58:12s23-124, 1996.

85. Poster presentation @ ADA 68th scientific session june 6-10 2008 – longitudinal study of diabetic autonomic dysfunction; corroboration of assessments -Melvyn J.Lafitte et al.

86. Khandedelwal E Indian Journal Physio Pharmacol;2011 Apr-Jun-55(2) 119-27.

87. Ramavat manish R prevalene of Cardiac Autonomic Neuropathy in patients with diabetes NJIRM;2012;3(3):15-19.

88. Viveka P Jyotsna, prevalene and pattern of cardiac autonomic dysfunction in newly detected Type 2 diabetes; diabetes research and clinical practice 1983-88.

# PROFORMA

- NAME : SL. NO:

- AGE /SEX:
- OCCUPATION:
- ADDRESS WITH CONTACT NUMBER:

- IP/OP NO:
- DATE OF ADMISSION:
- DATE OF DISCHARGE:

HISTORY:

Duration of diabetes

H/o chest pain , palpitations, syncope,dyspnoea,dizziness

H/o alcohol , smoking

Hypertension

Awareness of the disease and its complications

Physical examination

Sensorium

Pallor

Pedal edema

BP: PR:

CVS -

RS -

P/A -

CNS -

INVESTIGATIONS

CBC – TC,DC,ESR

HB, PLATELETS

BLOOD SUGAR

BLOOD UREA, SERUM CREATININE

TESTING FOR PERIPHERAL NEUROPATHY – VIBRATION AND 10 G MONOFILAMENT

URINE ROUTINE EXAMINATION

ECG

CARDIOVASCULAR REFLEX TESTS

- HEART RATE RESPONSE TO DEEP BREATHING, VALSALVA,STANDING
- BLOOD PRESSURE RESPONSE TO HANDGRIP AND STANDING

NON INVASIVE TESTING USING ANSISCOPE

# CONSENT FORM

1) I AGREE TO PARTICIPATE IN STUDY TITLED "PREVALENCE OF CARDIAC AUTONOMIC NEUROPATHY IN TYPE 2 DIABETIC PATIENTS"

2) I CONFIRM THAT I HAVE BEEN TOLD ABOUT THIS STUDY IN MY MOTHER TONGUE & HAVE HAD THE OPPURTUNITY TO ASK QUESTIONS

3) I UNDERSTAND THAT MY PARTIPATION IS VOLUNTERY & I MAY REFUSE TO PARTICIPATE AT ANY TIME WITHOUT GIVING ANY REASON AND WITHOUT AFFECTING MY BENEFITS.

4) I AGREE NOT TO RESTRICT THE USE OF ANY DATE OR RESULTS THAT ARISE FROM THE STUDY

5) I AGREE TO UNDERGO CLINICAL AUTONOMIC TESTING

NAME OF THE PARTICIPANT:

SIGN/THUMB PRINT INVESTIGATOR

| S.No. | Name | Age | Sex | Smoke | Years | HT | Peri neuro | Aware | Control | Ansisc | Sev | Vals | EI ratio | 30/15 st | ortho hyp | Conv | Sev |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | munusamy | 37 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 2 |  | n | n | n | 2 | 2 |  |
| 2 | thiyaga | 59 | 1 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 1 |
| 3 | amutha | 58 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 4 | sivagami | 50 | 2 | 2 | 3 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 5 | muniammal | 50 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 2 |  | 1 | 2 | 1 | 1 | 2 |  |
| 6 | shanthi | 48 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 |  | 2 | 2 | 1 | 1 | 1 | 1 |
| 7 | razia | 47 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 8 | bhagyam | 61 | 2 | 2 | 6 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 9 | krishnaveni | 60 | 2 | 2 | 5 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 10 | surya narayanan | 70 | 2 | 2 | 5 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 3 | 3 | 1 | 1 | 2 |
| 11 | mani | 60 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 12 | sherifa | 49 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 13 | maheswari | 50 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 14 | kousiya begum | 43 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 15 | shanmugam | 60 | 1 | 1 | 7 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 16 | subramani | 59 | 1 | 1 | 7 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 3 | 1 | 1 | 1 | 1 |
| 17 | sujatha | 38 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 18 | rajendiram | 49 | 1 | 2 | 5 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 3 | 3 | 1 | 1 | 2 |
| 19 | kala | 35 | 2 | 2 | 0 | 2 | 2 | 1 | 1 | 2 |  | 1 | 2 | 1 | 1 | 2 |  |
| 20 | vasudevan | 49 | 1 | 2 | 6 | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 2 | 3 | 1 | 1 | 1 |
| 21 | robert | 49 | 1 | 1 | 15 | 1 | 2 | 1 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 22 | alima bee | 51 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 1 | 1 | 2 |
| 23 | subair | 65 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 24 | bhoopalam | 71 | 1 | 2 | 12 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 25 | elizabeth | 40 | 2 | 2 | 5 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 26 | srinivasan | 44 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 |
| 27 | pachaiappan | 61 | 1 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 28 | rosemary | 45 | 2 | 2 | 7 | 2 | 1 | 2 | 2 | 1 | 2 | 3 | 1 | 3 | 2 | 1 | 2 |
| 29 | anandavalli | 45 | 2 | 2 | 3 | 2 | 1 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 30 | kuppu | 40 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 1 | 3 | 1 | 2 |  |
| 31 | manonmani | 53 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 |
| 32 | samiadiyal | 48 | 2 | 2 | 7 | 1 | 1 | 1 | 2 | 1 | 3 | 1 | 3 | 3 | 1 | 1 | 2 |
| 33 | subramani | 43 | 1 | 2 | 3 | 1 | 2 | 1 | 1 | 2 |  | 2 | 1 | 1 | 1 | 2 |  |
| 34 | bhoopalan | 71 | 1 | 2 | 4 | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 3 | 3 | 2 | 1 | 2 |
| 35 | muralidharam | 44 | 1 | 1 | 7 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 36 | mahalakshmi | 44 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 1 | 1 | 2 |
| 37 | nagaraj | 39 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 |  | 2 | 1 | 2 | 1 | 1 | 1 |
| 38 | krishnan | 56 | 1 | 2 | 5 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 1 |
| 39 | arun | 28 | 1 | 1 | 0 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 40 | vasanthi | 53 | 2 | 2 | 0 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 41 | ahmed | 52 | 1 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 42 | meenal | 32 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 3 | 1 | 1 | 1 |
| 43 | raman | 44 | 1 | 1 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 44 | asirvatham | 48 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 2 | 2 |

| | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 45 | selvi | 47 | 2 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 3 | 1 | 1 | 2 |
| 46 | logeswari | 35 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 2 | | 1 | 3 | 1 | 1 | 1 | 1 |
| 47 | balaraman | 65 | 1 | 1 | 5 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 48 | sarawwathy | 56 | 2 | 2 | 10 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 49 | vasuki | 38 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | | 2 | 1 | 2 | 1 | 1 | 1 |
| 50 | sukuna | 51 | 2 | 2 | 4 | 1 | 1 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 51 | meenal | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 2 | 2 | 1 | 1 |
| 52 | padmavathy | 70 | 2 | 2 | 10 | 2 | 2 | 1 | 1 | 1 | 3 | 3 | 3 | 2 | 3 | 1 | 3 |
| 53 | nagaraj | 41 | 1 | 1 | 0 | 2 | 2 | 2 | 1 | 1 | 3 | 2 | 3 | 3 | 2 | 1 | 2 |
| 54 | selvam | 50 | 1 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 55 | etiyappan | 41 | 1 | 2 | 6 | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 2 | 1 | 2 |
| 56 | rajeshwari | 58 | 2 | 2 | 5 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 57 | valli | 54 | 2 | 2 | 5 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 58 | kamalam | 55 | 2 | 2 | 4 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 59 | rajan | 45 | 1 | 2 | 0 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 2 |
| 60 | kuppuraj | 47 | 1 | 2 | 0 | 1 | 2 | 2 | 1 | 2 | | 1 | 1 | 2 | 1 | 2 | |
| 61 | meenal | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 3 | 3 | 1 | 1 | 2 |
| 62 | selvi | 47 | 2 | 2 | 0 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 63 | amudha | 40 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 1 | 1 | 2 |
| 64 | kannan | 51 | 1 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 65 | mariammal | 45 | 2 | 2 | 0 | 2 | 1 | 2 | 1 | 2 | | 1 | 2 | 3 | 1 | 1 | 1 |
| 66 | devaki | 52 | 2 | 2 | 10 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 67 | amudha | 47 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 68 | jyothi | 42 | 2 | 2 | 5 | 1 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 69 | meena | 45 | 2 | 2 | 0 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 70 | krishnamoorthy | 57 | 1 | 2 | 20 | 1 | 1 | 1 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 71 | chellammal | 61 | 2 | 2 | 29 | 1 | 1 | 1 | 2 | 1 | 3 | 3 | 3 | 2 | 1 | 1 | 2 |
| 72 | kanniappan | 34 | 1 | 2 | 4 | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 73 | mariappa | 63 | 2 | 2 | 5 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 74 | kuppan | 60 | 1 | 1 | 10 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 75 | parameswari | 42 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 76 | kalyani | 55 | 2 | 2 | 11 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 77 | annal | 65 | 2 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 2 | 1 | 1 | 2 |
| 78 | gomathy | 34 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | | 1 | 2 | 1 | 1 | 2 | |
| 79 | seetha | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 80 | rojammal | 55 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 2 | | 2 | 1 | 2 | 1 | 1 | 1 |
| 81 | gangammal | 55 | 2 | 2 | 8 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 82 | selvi | 52 | 2 | 2 | 4 | 1 | 2 | 2 | 1 | 2 | | 2 | 2 | 1 | 1 | 1 | 1 |
| 83 | damodaran | 45 | 1 | 1 | 0 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 2 | 1 | 1 | 1 |
| 84 | kasiammal | 42 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 2 | | 1 | 2 | 1 | 1 | 2 | |
| | | | 1-M | 1-YES | | 1-y | 1-yes | 1- yes | 1-yes | 1- can +ve | 1- early | 1 -N | 1 -N | 1 -N | 1 -N | 1- can +ve | 1- early |
| | | | | | | | | | | | 2- late | 2-BL | 2-BL | 2-BL | 2-BL | | 2- definit |
| | | | | | | | | | | | 3- adv | 3-abn | 3-abn | 3-abn | 3-abn | | 3- adv |

| S.No. | Name | Age | Sex | Smoke | Years | HT | Peri neuro | Aware | Control | Ansisc | Sev | Vals | EI ratio | 30/15 st | ortho hyp | Conv | Sev |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | munusamy | 37 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 2 |  | n | n | n | 2 | 2 |  |
| 2 | thiyaga | 59 | 1 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 1 |
| 3 | amutha | 58 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 4 | sivagami | 50 | 2 | 2 | 3 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 5 | muniammal | 50 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 2 |  | 1 | 2 | 1 | 1 | 2 |  |
| 6 | shanthi | 48 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 |  | 2 | 2 | 1 | 1 | 1 | 1 |
| 7 | razia | 47 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 8 | bhagyam | 61 | 2 | 2 | 6 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 9 | krishnaveni | 60 | 2 | 2 | 5 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 10 | surya narayanan | 70 | 2 | 2 | 5 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 3 | 3 | 1 | 1 | 2 |
| 11 | mani | 60 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 12 | sherifa | 49 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 13 | maheswari | 50 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 14 | kousiya begum | 43 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 15 | shanmugam | 60 | 1 | 1 | 7 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 16 | subramani | 59 | 1 | 1 | 7 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 3 | 1 | 1 | 1 | 1 |
| 17 | sujatha | 38 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 18 | rajendiram | 49 | 1 | 2 | 5 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 3 | 3 | 1 | 1 | 2 |
| 19 | kala | 35 | 2 | 2 | 0 | 2 | 2 | 1 | 1 | 2 |  | 1 | 2 | 1 | 1 | 2 |  |
| 20 | vasudevan | 49 | 1 | 2 | 6 | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 2 | 3 | 1 | 1 | 1 |
| 21 | robert | 49 | 1 | 1 | 15 | 1 | 2 | 1 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 22 | alima bee | 51 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 1 | 1 | 2 |
| 23 | subair | 65 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 24 | bhoopalam | 71 | 1 | 2 | 12 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 25 | elizabeth | 40 | 2 | 2 | 5 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 26 | srinivasan | 44 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 |
| 27 | pachaiappan | 61 | 1 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 28 | rosemary | 45 | 2 | 2 | 7 | 2 | 1 | 2 | 2 | 1 | 2 | 3 | 1 | 3 | 2 | 1 | 2 |
| 29 | anandavalli | 45 | 2 | 2 | 3 | 2 | 1 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 30 | kuppu | 40 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 1 | 3 | 1 | 2 |  |
| 31 | manonmani | 53 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 |
| 32 | samiadiyal | 48 | 2 | 2 | 7 | 1 | 1 | 1 | 2 | 1 | 3 | 1 | 3 | 3 | 1 | 1 | 2 |
| 33 | subramani | 43 | 1 | 2 | 3 | 1 | 2 | 1 | 1 | 2 |  | 2 | 1 | 1 | 1 | 2 |  |
| 34 | bhoopalan | 71 | 1 | 2 | 4 | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 3 | 3 | 2 | 1 | 2 |
| 35 | muralidharam | 44 | 1 | 1 | 7 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 36 | mahalakshmi | 44 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 1 | 1 | 2 |
| 37 | nagaraj | 39 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 |  | 2 | 1 | 2 | 1 | 1 | 1 |
| 38 | krishnan | 56 | 1 | 2 | 5 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 1 |
| 39 | arun | 28 | 1 | 1 | 0 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 40 | vasanthi | 53 | 2 | 2 | 0 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 41 | ahmed | 52 | 1 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 42 | meenal | 32 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 3 | 1 | 1 | 1 |
| 43 | raman | 44 | 1 | 1 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 44 | asirvatham | 48 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 2 | 2 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 45 | selvi | 47 | 2 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 3 | 1 | 1 | 2 |
| 46 | logeswari | 35 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 2 | | 1 | 3 | 1 | 1 | 1 | 1 |
| 47 | balaraman | 65 | 1 | 1 | 5 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 48 | sarawwathy | 56 | 2 | 2 | 10 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 49 | vasuki | 38 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | | 2 | 1 | 2 | 1 | 1 | 1 |
| 50 | sukuna | 51 | 2 | 2 | 4 | 1 | 1 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 51 | meenal | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 2 | 2 | 1 | 1 |
| 52 | padmavathy | 70 | 2 | 2 | 10 | 2 | 2 | 1 | 1 | 1 | 3 | 3 | 3 | 2 | 3 | 1 | 3 |
| 53 | nagaraj | 41 | 1 | 1 | 0 | 2 | 2 | 2 | 1 | 1 | 3 | 2 | 3 | 3 | 2 | 1 | 2 |
| 54 | selvam | 50 | 1 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 55 | etiyappan | 41 | 1 | 2 | 6 | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 2 | 1 | 2 |
| 56 | rajeshwari | 58 | 2 | 2 | 5 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 57 | valli | 54 | 2 | 2 | 5 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 58 | kamalam | 55 | 2 | 2 | 4 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 59 | rajan | 45 | 1 | 2 | 0 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 2 |
| 60 | kuppuraj | 47 | 1 | 2 | 0 | 1 | 2 | 2 | 1 | 2 | | 1 | 1 | 2 | 1 | 2 | |
| 61 | meenal | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 3 | 3 | 1 | 1 | 2 |
| 62 | selvi | 47 | 2 | 2 | 0 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 63 | amudha | 40 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 1 | 1 | 2 |
| 64 | kannan | 51 | 1 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 65 | mariammal | 45 | 2 | 2 | 0 | 2 | 1 | 2 | 1 | 2 | | 1 | 2 | 3 | 1 | 1 | 1 |
| 66 | devaki | 52 | 2 | 2 | 10 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 67 | amudha | 47 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 68 | jyothi | 42 | 2 | 2 | 5 | 1 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 69 | meena | 45 | 2 | 2 | 0 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 70 | krishnamoorthy | 57 | 1 | 2 | 20 | 1 | 1 | 1 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 71 | chellammal | 61 | 2 | 2 | 29 | 1 | 1 | 1 | 2 | 1 | 3 | 3 | 3 | 2 | 1 | 1 | 2 |
| 72 | kanniappan | 34 | 1 | 2 | 4 | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 73 | mariappa | 63 | 2 | 2 | 5 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 74 | kuppan | 60 | 1 | 1 | 10 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 75 | parameswari | 42 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 76 | kalyani | 55 | 2 | 2 | 11 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 77 | annal | 65 | 2 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 2 | 1 | 1 | 2 |
| 78 | gomathy | 34 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | | 1 | 2 | 1 | 1 | 2 | |
| 79 | seetha | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 80 | rojammal | 55 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 2 | | 2 | 1 | 2 | 1 | 1 | 1 |
| 81 | gangammal | 55 | 2 | 2 | 8 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 82 | selvi | 52 | 2 | 2 | 4 | 1 | 2 | 2 | 1 | 2 | | 2 | 2 | 1 | 1 | 1 | 1 |
| 83 | damodaran | 45 | 1 | 1 | 0 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 2 | 1 | 1 | 1 |
| 84 | kasiammal | 42 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 2 | | 1 | 2 | 1 | 1 | 2 | |
| | | | 1-M | 1-YES | | 1-y | 1-yes | 1- yes | 1-yes | 1- can +ve | 1- early | 1 -N | 1 -N | 1 -N | 1 -N | 1- can +ve | 1- early |
| | | | | | | | | | | | 2- late | 2-BL | 2-BL | 2-BL | 2-BL | | 2- definit |
| | | | | | | | | | | | 3- adv | 3-abn | 3-abn | 3-abn | 3-abn | | 3- adv |

| S.No. | Name | Age | Sex | Smoke | Years | HT | Peri neuro | Aware | Control | Ansisc | Sev | Vals | EI ratio | 30/15 st | ortho hyp | Conv | Sev |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | munusamy | 37 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 2 |  | n | n | n | 2 | 2 |  |
| 2 | thiyaga | 59 | 1 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 1 | 1 |
| 3 | amutha | 58 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 4 | sivagami | 50 | 2 | 2 | 3 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 5 | muniammal | 50 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 2 |  | 1 | 2 | 1 | 1 | 2 |  |
| 6 | shanthi | 48 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 |  | 2 | 2 | 1 | 1 | 1 | 1 |
| 7 | razia | 47 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 8 | bhagyam | 61 | 2 | 2 | 6 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 9 | krishnaveni | 60 | 2 | 2 | 5 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 10 | surya narayanan | 70 | 2 | 2 | 5 | 2 | 1 | 1 | 1 | 1 | 2 | 1 | 3 | 3 | 1 | 1 | 2 |
| 11 | mani | 60 | 1 | 2 | 1 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 12 | sherifa | 49 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 13 | maheswari | 50 | 2 | 2 | 2 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 14 | kousiya begum | 43 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 15 | shanmugam | 60 | 1 | 1 | 7 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 16 | subramani | 59 | 1 | 1 | 7 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 3 | 1 | 1 | 1 | 1 |
| 17 | sujatha | 38 | 2 | 2 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 18 | rajendiram | 49 | 1 | 2 | 5 | 1 | 2 | 1 | 1 | 1 | 1 | 2 | 3 | 3 | 1 | 1 | 2 |
| 19 | kala | 35 | 2 | 2 | 0 | 2 | 2 | 1 | 1 | 2 |  | 1 | 2 | 1 | 1 | 2 |  |
| 20 | vasudevan | 49 | 1 | 2 | 6 | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 2 | 3 | 1 | 1 | 1 |
| 21 | robert | 49 | 1 | 1 | 15 | 1 | 2 | 1 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 22 | alima bee | 51 | 2 | 2 | 1 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 1 | 1 | 2 |
| 23 | subair | 65 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 24 | bhoopalam | 71 | 1 | 2 | 12 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 25 | elizabeth | 40 | 2 | 2 | 5 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 26 | srinivasan | 44 | 1 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 1 | 1 | 3 | 1 | 1 | 1 | 1 |
| 27 | pachaiappan | 61 | 1 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 3 | 3 | 2 | 1 | 1 | 2 |
| 28 | rosemary | 45 | 2 | 2 | 7 | 2 | 1 | 2 | 2 | 1 | 2 | 3 | 1 | 3 | 2 | 1 | 2 |
| 29 | anandavalli | 45 | 2 | 2 | 3 | 2 | 1 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 30 | kuppu | 40 | 2 | 2 | 3 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 1 | 3 | 1 | 2 |  |
| 31 | manonmani | 53 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 2 | 1 | 1 | 1 |
| 32 | samiadiyal | 48 | 2 | 2 | 7 | 1 | 1 | 1 | 2 | 1 | 3 | 1 | 3 | 3 | 1 | 1 | 2 |
| 33 | subramani | 43 | 1 | 2 | 3 | 1 | 2 | 1 | 1 | 2 |  | 2 | 1 | 1 | 1 | 2 |  |
| 34 | bhoopalan | 71 | 1 | 2 | 4 | 1 | 1 | 2 | 1 | 1 | 2 | 1 | 3 | 3 | 2 | 1 | 2 |
| 35 | muralidharam | 44 | 1 | 1 | 7 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 36 | mahalakshmi | 44 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 1 | 1 | 2 |
| 37 | nagaraj | 39 | 1 | 1 | 1 | 2 | 2 | 2 | 2 | 2 |  | 2 | 1 | 2 | 1 | 1 | 1 |
| 38 | krishnan | 56 | 1 | 2 | 5 | 2 | 2 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 1 | 1 | 1 |
| 39 | arun | 28 | 1 | 1 | 0 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 40 | vasanthi | 53 | 2 | 2 | 0 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 41 | ahmed | 52 | 1 | 1 | 0 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 42 | meenal | 32 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 1 | 2 | 1 | 3 | 1 | 1 | 1 |
| 43 | raman | 44 | 1 | 1 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 44 | asirvatham | 48 | 2 | 2 | 2 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 2 | 2 |

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|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 45 | selvi | 47 | 2 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 3 | 3 | 1 | 1 | 2 |
| 46 | logeswari | 35 | 2 | 2 | 3 | 1 | 2 | 2 | 1 | 2 | | 1 | 3 | 1 | 1 | 1 | 1 |
| 47 | balaraman | 65 | 1 | 1 | 5 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 48 | sarawwathy | 56 | 2 | 2 | 10 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 49 | vasuki | 38 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | | 2 | 1 | 2 | 1 | 1 | 1 |
| 50 | sukuna | 51 | 2 | 2 | 4 | 1 | 1 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 51 | meenal | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 1 | 1 | 2 | 3 | 2 | 2 | 1 | 1 |
| 52 | padmavathy | 70 | 2 | 2 | 10 | 2 | 2 | 1 | 1 | 1 | 3 | 3 | 3 | 2 | 3 | 1 | 3 |
| 53 | nagaraj | 41 | 1 | 1 | 0 | 2 | 2 | 2 | 1 | 1 | 3 | 2 | 3 | 3 | 2 | 1 | 2 |
| 54 | selvam | 50 | 1 | 2 | 0 | 2 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 55 | etiyappan | 41 | 1 | 2 | 6 | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 2 | 2 | 1 | 2 |
| 56 | rajeshwari | 58 | 2 | 2 | 5 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 57 | valli | 54 | 2 | 2 | 5 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 58 | kamalam | 55 | 2 | 2 | 4 | 2 | 2 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 59 | rajan | 45 | 1 | 2 | 0 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 2 |
| 60 | kuppuraj | 47 | 1 | 2 | 0 | 1 | 2 | 2 | 1 | 2 | | 1 | 1 | 2 | 1 | 2 | |
| 61 | meenal | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 2 | 1 | 2 | 1 | 3 | 3 | 1 | 1 | 2 |
| 62 | selvi | 47 | 2 | 2 | 0 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 63 | amudha | 40 | 2 | 2 | 1 | 1 | 2 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 1 | 1 | 2 |
| 64 | kannan | 51 | 1 | 1 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 65 | mariammal | 45 | 2 | 2 | 0 | 2 | 1 | 2 | 1 | 2 | | 1 | 2 | 3 | 1 | 1 | 1 |
| 66 | devaki | 52 | 2 | 2 | 10 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 67 | amudha | 47 | 2 | 2 | 1 | 2 | 1 | 2 | 1 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 68 | jyothi | 42 | 2 | 2 | 5 | 1 | 2 | 2 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 69 | meena | 45 | 2 | 2 | 0 | 1 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 70 | krishnamoorthy | 57 | 1 | 2 | 20 | 1 | 1 | 1 | 1 | 1 | 3 | 3 | 3 | 3 | 2 | 1 | 2 |
| 71 | chellammal | 61 | 2 | 2 | 29 | 1 | 1 | 1 | 2 | 1 | 3 | 3 | 3 | 2 | 1 | 1 | 2 |
| 72 | kanniappan | 34 | 1 | 2 | 4 | 2 | 2 | 2 | 2 | 1 | 3 | 3 | 3 | 3 | 3 | 1 | 3 |
| 73 | mariappa | 63 | 2 | 2 | 5 | 1 | 1 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 2 | 1 | 2 |
| 74 | kuppan | 60 | 1 | 1 | 10 | 1 | 1 | 2 | 2 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 75 | parameswari | 42 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 76 | kalyani | 55 | 2 | 2 | 11 | 2 | 1 | 1 | 1 | 1 | 2 | 2 | 2 | 3 | 1 | 1 | 1 |
| 77 | annal | 65 | 2 | 2 | 4 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 2 | 1 | 1 | 2 |
| 78 | gomathy | 34 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | | 1 | 2 | 1 | 1 | 2 | |
| 79 | seetha | 60 | 2 | 2 | 3 | 2 | 2 | 2 | 1 | 1 | 2 | 2 | 3 | 3 | 1 | 1 | 2 |
| 80 | rojammal | 55 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 2 | | 2 | 1 | 2 | 1 | 1 | 1 |
| 81 | gangammal | 55 | 2 | 2 | 8 | 1 | 1 | 2 | 2 | 1 | 2 | 3 | 3 | 3 | 2 | 1 | 2 |
| 82 | selvi | 52 | 2 | 2 | 4 | 1 | 2 | 2 | 1 | 2 | | 2 | 2 | 1 | 1 | 1 | 1 |
| 83 | damodaran | 45 | 1 | 1 | 0 | 1 | 2 | 2 | 2 | 1 | 2 | 2 | 3 | 2 | 1 | 1 | 1 |
| 84 | kasiammal | 42 | 2 | 2 | 0 | 2 | 2 | 2 | 1 | 2 | | 1 | 2 | 1 | 1 | 2 | |
| | | | 1-M | 1-YES | | 1-y | 1-yes | 1- yes | 1-yes | 1- can +ve | 1- early | 1 -N | 1 -N | 1 -N | 1 -N | 1- can +ve | 1- early |
| | | | | | | | | | | | 2- late | 2-BL | 2-BL | 2-BL | 2-BL | | 2- definit |
| | | | | | | | | | | | 3- adv | 3-abn | 3-abn | 3-abn | 3-abn | | 3- adv |